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ANNALS
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XXV

SECRETORY SIALOGRAPHY IN DISEASES OF THE MAJOR SALIVARY GLANDS

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Sialography is the process of demonstrating roentgenographically the duct system of the salivary glands after the injection of radiopaque media. Since the introduction of this technique by Barsony[1] few changes in the procedure have been suggested. Recently, however, in order to achieve a more comprehensive understanding of the physiology of the normal gland a modification of the technique has been adopted in which the duct system is filled with media immediately emptied and again examined roentgenographically. Evacuation of the contrast material is facilitated by increasing the flow of saliva induced by reflex stimulation of the glands. Postevacuation films have revealed patterns which have been of assistance in differentiating normal and diseased conditions. This method, termed physiological or secretory sialography,[2,3] has been used to investigate a broad range of clinical cases and to establish criteria for roentgen studies of the salivary glands in health and disease.

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This study was aided by the Frank D. McKay Research Fund in Otolaryngology.

The technique of secretory sialography has been applied to patients with various diseases of the major salivary glands. This report, based on the analysis of 135 cases involving more than 200 sialograms, correlates the clinical, pathological, and sialographic observtions made with the modified technique.

INFLAMMATORY DISEASES OF THE SALIVARY GLANDS

Sialography is contraindicated in all acute inflammatory diseases, since the insertion of instruments and injection of foreign material into the duct system is deleterious. In chronic non-neoplastic swellings of the major salivary glands, however, sialography can be most helpful in the problem of differential diagnosis. Among the inflammatory diseases and agents listed in the literature are:

Chronic recurrent sialodochoparotitis
Calculi and foreign bodies in the ducts
Specific infections such as tuberculosis and actinomycosis
Mikulicz's disease
Sjögren's disease or the "sicca syndrome"
Lymphoblastoma
Boeck's sarcoid
Hereditary familial hyperplasia
Hyperplasia associated with endocrine changes (menstrual cycle)
"Salivary retention" in the newborn
Post-mumps sialadenitis
Drug intoxication such as lead, iodine, copper, and opium
Allergy
Strictures of the ducts
Traumatic lesions

This long list prompts one to seek a simpler classification as a basis for correlating the sialograms with the clinical findings. It is therefore suggested that for purposes of sialography, chronic inflammatory enlargements of the salivary glands be divided into two general groups:

1. Chronic obstructive sialodochiectasis (abnormalities primarily in the main duct).

2. Chronic nonobstructive sialodochiectasis (abnormalities primarily in the peripheral ducts).

Chronic Obstructive Sialodochiectasis. There appears to be a fundamental difference between the pathogenesis of parotid and submaxillary gland swellings and the resultant sialographic pattern. Infection of the submaxillary gland usually is associated with calculi,[4,5] whereas parotitis is more commonly nonobstructive. This is confirmed by the frequent sialographic finding of dilation of Wharton's duct and its primary divisions, in contrast to the rarity of peripheral duct dilation. There are two main subdivisions of obstructive agents in salivary gland disease: calculi and strictures.

Scout Films: The most common cause of obstruction to salivary flow is the presence of calculi which in the majority of cases are readily identified on preliminary films. Nevertheless, sialograms are indicated for three reasons, if duct obstruction is present: 1) If the calculus is opaque, the knowledge of its position in relation to the gland parenchyma and the duct will aid in planning its surgical removal. 2) Approximately 20 per cent of salivary calculi are nonopaque[6] and can only be detected by sialography. 3) Strictures of the duct and papilla can be identified.[7]

Filling Phase: Although the most important finding is dilation of the main duct (Wharton's or Stensen's duct) and the primary and secondary ramifications, it should be recognized that small calculi (1 to 3 mm) are usually nonobstructive and radiolucent. These small calculi are easily overlooked, since they may be mistaken for injected air bubbles, particularly when associated with larger nonopaque calculi.

If the main duct is dilated throughout, a history of repeated episodes of passage of stones usually can be elicited. Dilation of the duct will occur proximal to the stone, which can be forced back into the duct upon retrograde injection of contrast material, permitting visualization of the peripheral ducts (Fig. 1). In early cases without evidence of infection the peripheral ducts may appears to be normal. In chronic cases, loss of the arboreal pattern of the normal gland is seen as a result of atrophy of the parenchyma. The pattern of nonobstructive sialodochiectasis is not seen when secondary infection occurs. The dilated main duct, the loss of terminal arborization, and the irregular distribution of small collections of contrast material suggest abscesses rather than sialectasis, and serve to differentiate this condition from recurrent nonobstructive sialadenitis. Occasionally calculi may erode the wall of the main duct. If the calculi are extraglandular they form pseudodiverticula, but if they are intraglandular, atypical abscesses and granulomas may result (Fig. 2). When total obstruction has occurred, probing the duct may be insufficient to rule out stricture; here sialography is a valuable aid in establishing the diagnosis.

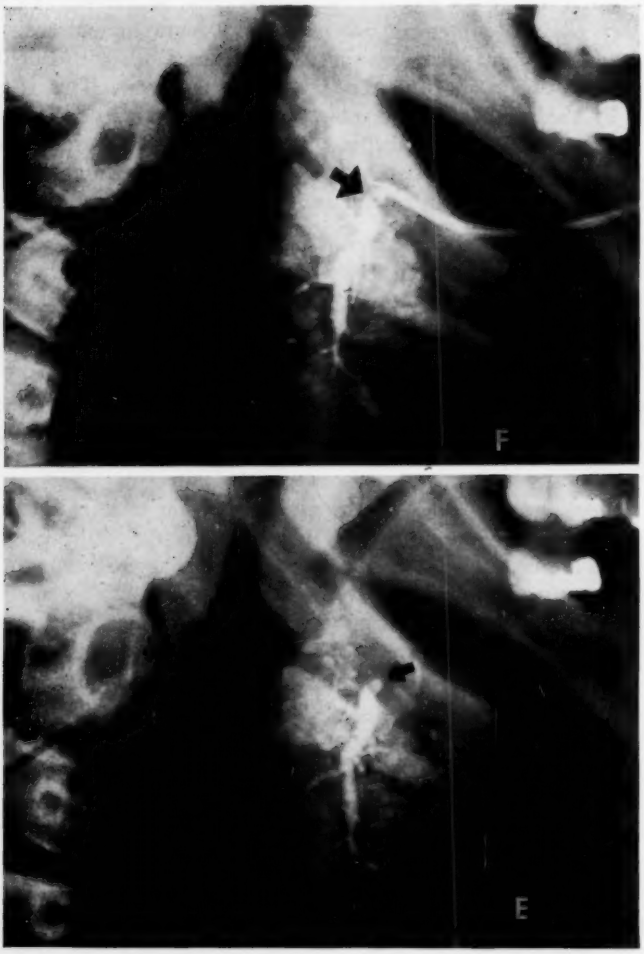

Fig. 1.—Sialogram of a submaxillary calculus. The FILLING PHASE demonstrates a calculus near the hilum of the gland, lodged in the proximal dilated portion of Wharton's duct. The EMPTYING PHASE shows that upon stimulation, the salivary flow forces the stone into the narrower, distal portion of Wharton's duct. This post stimulation film demonstrates the ball-valve mechanism of obstruction to salivary flow which is the basis of acute pain and swelling precipitated by eating.

Strictures at the duct orifice may lead to considerable dilation and tortuosity of the main salivary channel. The dilation of the papillary orifice caused by inserting the catheter for a sialogram may cure the patient. Multiple strictures following a severe case of pneumococcal parotitis have led to a "sausage-string" appearance of Stensen's duct.[6]

Secretory Phase: Although poststimulation films are of limited clinical value in this disease, they demonstrate some changes which may explain the symptoms and the process of dilation of the main duct. The ball-valve mechanism illustrated in Figure 1 demonstrates the basis for pain and swelling which may be precipitated by eating. The continual pressure exerted by salivary flow may force the stone from the duct, but in the process the accumulated secretions cause dilation of the ducts.

Pathologic Correlation: The histologic findings in obstructive sialodochiectasis are unlike those seen in case of nonobstructive disease. The ducts that are dilated are the main duct and the larger interlobar and interlobular septal channels (Fig. 3). In cases where obstruction has been of short duration, the acinar tissue and peripheral ducts may be normal. In advanced cases, as complete block supervenes, scarring and fatty atrophy of the gland predominate. The intralobular ducts are obliterated, accounting for the loss of the arboreal sialographic pattern.

Chronic Nonobstructive Sialodochiectasis (Sialectasis). This heterogeneous group of diseases appears to have a common roentgenographic-histologic denominator, as indicated by the correlation of sialographic findings with the pathologic changes.

Mikulicz's Disease: In 1892, Mikulicz[8] described a patient with benign, asymptomatic, symmetrical enlargement of the lacrimal and salivary glands. Histologic examination of excised submaxillary gland tissue disclosed replacement of the glandular parenchyma by lymphoid tissue. In the years that followed, Mikulicz's disease became a confused subject, for it was soon apparent that the illness ran a benign and self-limited course in some patients, while it was rapidly fatal in others. Attempted etiological classifications, with differentiation between Mikulicz's disease proper and Mikulicz's syndrome,[9,10] served to enhance the confusion. In contrast to the original contention that the disease is always bilateral and involves the lacrimal glands is the report of Morgan and Castleman[11] indicating that the disease can have a unilateral distribution usually confined to the salivary glands alone. Investigators[12,13] who have applied sialographic techniques to the diagnosis of Mikulicz's disease have reported essentially normal radiographic patterns of the salivary duct system. It

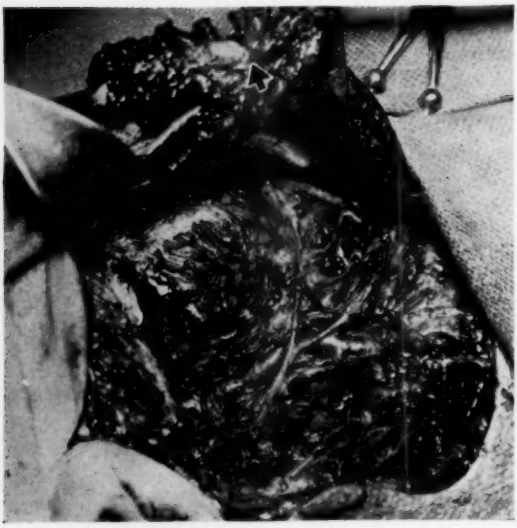

Fig. 2.—A parotid calculus (arrow) which eroded the wall of Stenson's duct and lodged in the gland substance. This resulted in a chronic infectious granuloma which required total parotidectomy.

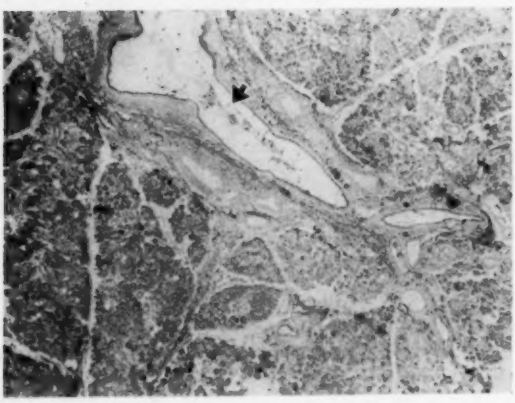

Fig. 3.—Pathologic correlation of obstructive salivary gland disease with sialograms. The microscopic section shows dilation of the interlobar and interlobular ducts (*arrow*). The intralobular ducts are not enlarged.

would appear that the discrepancy between the assumed histologic picture of Mikulicz's disease and the finding of a normal sialogram is due to the infrequency with which biopsy specimens have been obtained for certification of the clinical impression.

Recurrent Sialadenitis in Children: With the advent of sialography, a group of cases was separated from the Mikulicz category and the term "sialectasis" was applied because the roentgenographic finding of dilated terminal ducts was similar to that of bronchiectasis as visualized in bronchograms. The first recorded cases were those reported by Keith[14] and Pyrrah and Allison,[15] both of these cases occurring in children. Excellent reports of recurrent sialadenitis in children were presented by Londe and Pelz[16] in 1933 and by Pearson[17] in 1935. Analysis of the 31 cases reported by these authors revealed that the age incidence ranged from one month to 16 years and that the sexes were equally represented. The salivary gland usually involved is the parotid, either on one side or both, separately or simultaneously. The swelling has a tendency to recur and to be painful, particularly during and after meals. It may last from hours to days, the gland remaining moderately enlarged between exacerbations. The salivary gland is tense and tender during the acute episode but firm and nodular between attacks. Pressure on the gland may cause frank pus or plugs of turbid-gelatinous saliva to appear at the orifice of the Stensen's duct. Bacteriologic examination reveals the pneumococcus in pure culture, often type 17. The patterns of sialectasis are diagnostic of this condition.

Recurrent Pyogenic Parotitis in Adults: Between 1931 and 1940, Payne recorded[18,19,20] his extensive experience with sialography in patients with recurrent pyogenic parotitis, the majority of whom were women approaching or experiencing the menopause. His article on a series of 208 cases, published in 1937, is one of the most carefully documented reports in the literature. Recurrent, tense swelling of the parotid glands is the predominant symptom in this disease. The onset often is insidious and preceded by a febrile episode, but in some instances the enlargement may be brought to the patient's attention suddenly while eating. Although the parotid swelling usually is bilateral, one side may be more severely involved in some cases. The submaxillary glands also may be affected in long-standing disease. The enlargement persists usually from three to ten days, although periods of two or three months have been recorded. At first the swelling subsides completely between attacks, leaving only a minimal residual mass. Later, however, the swelling persists and the gland is diffusely palpable. The surface is nodular and the gland rubbery in consistency. Saliva expressed from Stensen's duct is scanty, inspis-

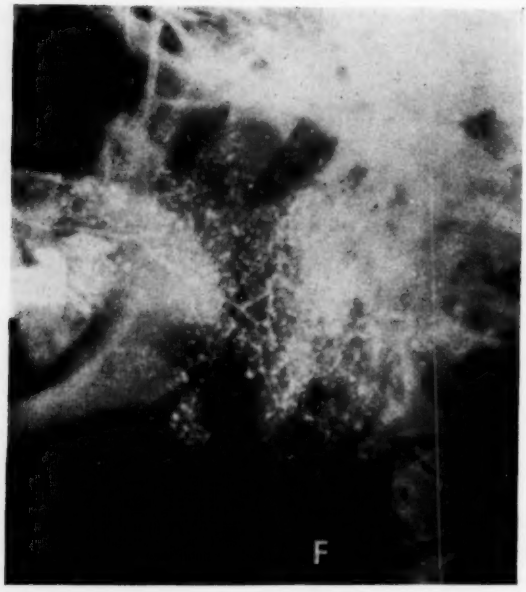

Fig. 4.—Sialogram of recurrent pyogenic parotitis in adults. FILLING PHASE. The parotid gland (right) shows a diffuse punctate dilation of the peripheral ducts and a striking decrease in the number of more proximal intraglandular ducts.

sated, and gelatinous. Bacteriologic examination of material taken directly from this duct often reveals *Staphylococcus viridans*. It would appear that this disease represents an incomplete form of the sicca syndrome of Sjögren which later may develop fully, to complete the clinical picture of the latter disease.

Sjögren's Syndrome: In 1932 Henrik Sjögren[21] described a chronic, progressive disease characterized by a filamentary keratitis and conjunctivitis (keratoconjunctivitis sicca), dryness of the mucous membranes of the nose, mouth, and throat (rhinopharyngolaryngitis sicca), enlargement or atrophy of the parotid glands (sialoadenopathia atrophicans), and rheumatoid polyarthritis.[22,23] The condition usually occurs in women in the fourth and fifth decades of life. The exact cause of the sicca syndrome is not known; however, a double etiology of infection and endocrine disturbance appears to be worthy of consideration. The pattern of sialectasis has been demonstrated in

all of our patients with the sicca syndrome. Morgan has attempted to provide a connecting link between Mikulicz's disease and Sjögren's syndrome. After a review of the available pathological material and the original histologic sections collected by Sjögren, it was suggested that the histologic conditions in the two diseases were similar.

Apparently no previous attempt has been made to explain why this diversified group of diseases yields the similar and characteristic roentgenographic pattern of sialectasis. The reason seems to be that because of the inflammatory nature of the disease most workers did not perform biopsies in such cases. We believe that biopsy examinations are necessary for insight into the nature of the underlying pathologic process. The correlation of microscopic findings with sialograms has helped to explain some of the variations and similarities noted.

Scout Films: The preliminary films generaly show soft tissue swelling. In advanced cases, scattered fine nodular calcific densities are seen in the gland. The most striking case of diffuse calcinosis of the parotid glands was reported by Payne in a 30-year-old woman with associated Raynaud's phenomenon and scleroderma.

Filling Phase: The following classification, which incorporates the reports in the literature[18,24] as well as our own observations, is proposed:

1. Punctate: The earliest findings are characterized by a diffuse punctate dilation of the peripheral ducts that are less than 1 mm in size. The main duct is of normal caliber, but a striking decrease in the number of the intraglandular ducts is immediately apparent (Fig. 4). Careful examination shows that the lumina of the second- to fourth-order peripheral ducts are narrowed to fine linear channels. The entire gland parenchyma is involved, including the accessory lobe if it is present.

2. Globular: In moderately advanced disease, the globules of contrast material increase to 1 to 2 mm in diameter but remain uniform in size and distribution. The main duct still remains normal in caliber, but the intraglandular duct divisions are no longer seen. The appearance is that of a branchless, fruit-laden tree, and has been referred to in the literature as the "mulberry" pattern (Fig. 5).

3. Cavitary: In advanced stages, there is a coalescence of these globules, which now become irregular in size and distribution and decreased in number. Filling defects suggesting cystic dilation are noted (Fig. 6).

4. Destructive: In the end stages, there is a bizarre pattern which suggests invasion and destruction of the gland parenchyma

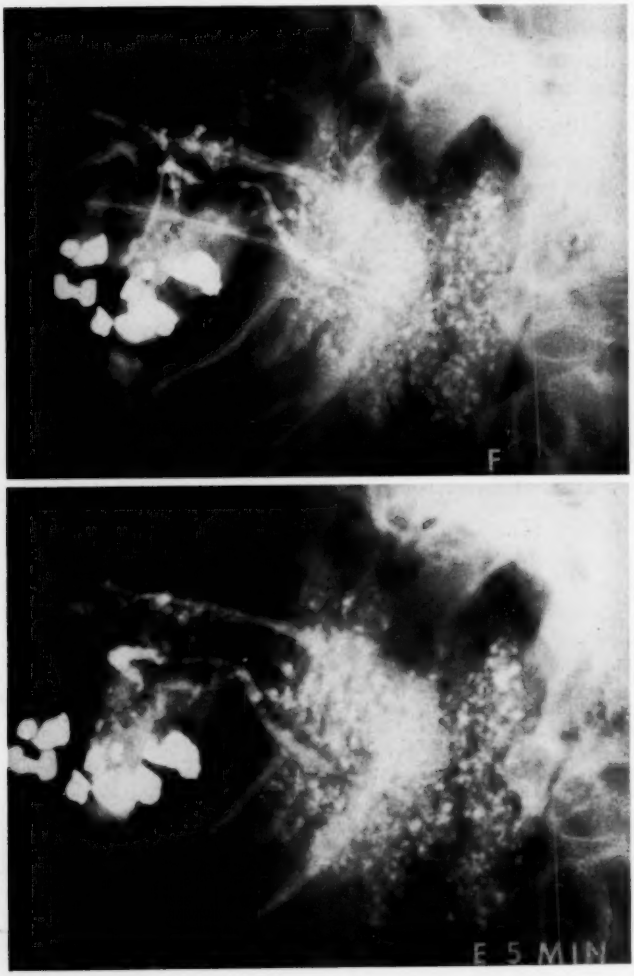

Fig. 5.—Sialogram of Sjögren's Syndrome. In the FILLING PHASE, the typical mulberry pattern of the globular stage of sialectasis is present. The accessory lobe of the parotid gland is also involved. In the 5 MINUTE POST EVACUATION film, the lack of salivary flow is verified by the unaltered appearance of the sialogram.

by neoplasm. The differential point at this stage is the fact that other glands, whether swollen or not, will show the manifestations of sialectasis (Fig. 7).

Emptying Phase: The degree of emptying following stimulation adds to the knowledge of the altered physiology in the diseased gland. The retention of the contrast material in the terminal ducts is due to the inability of the secretory pressure of the acini to overcome the resistance offered by the narrowed interstitial or septal ducts. As a result, the retained fluid causes dilation of the intralobular ducts. The larger the size of the retained globule, the greater the obstruction and the slower the emptying of the contrast material. Serial films taken at intervals of five minutes, one-half hour, one hour and 24 hours permit evaluation of the degree of secretory function in cases where scant flow exists (Fig. 5). The failure of Stenson's duct to empty as shown in the five minute stimulation film is in keeping with the degree of xerostomia seen clinically. The bizarre pattern of the end stage remains unchanged for days to weeks, since no acinar tissue remains and the contrast material has permeated the gland septa.

Pathologic Correlation: The constant finding in sections of tissue from patients with chronic nonobstructive sialodochiectasis is that of an inflammatory response regardless of whether the irritant is an infectious agent, an allergic or hyperimmune phenomenon, or chemical injected into the ducts. The tissue response is the same with infiltrations of leukocytes and lymphocytes into the interstitial septa of the gland. The inflammatory changes have three features—exudation, proliferation, and retrogression. The changes differ in intensity depending on the duration of the disease.

The earliest finding in chronic sialadenitis is lymphocytic infiltration around the interlobar and particularly the interlobular ducts in the septa of the salivary gland. Following this stage of exudation, proliferation of fibroblasts occurs and collagen fibers appear. In recurrent parotitis in children and adults, the scarring increases following exacerbations and results in stenosis of the interlobular ducts. Although we had only two biopsy reports from this group of cases in our series, Tietze[25] and Thaysen,[26] who obtained parotid glands from a 4-months-old infant and from a 3-year-old child respectively, have reported the same microscopic features. Both authors described a marked increase in interlobular connective tissue, with fibrous tissue replacement of the lobules and marked inflammatory cellular infiltrations.

In Mikulicz's and Sjögren's diseases there is an element of epithelial and myoepithelial cell hyperplasia which also tends to narrow the lumina of the interlobular ducts. Functioning acinar tissue con-

Fig. 6.—Sialogram of recurrent pyogenic parotitis in adults. FILLING PHASE. The parotid gland shows irregular cystic cavities replacing the normal duct pattern. This is the left parotid gland of the patient shown in Figure 4.

tinues to secrete against a narrowed duct system, resulting in retention of some saliva in the intralobular ducts, which then dilate. It is at this stage that the sialographic findings of terminal duct dilation and lack of intraglandular branching correlate well with the sparsity of interlobular and interlobar ducts located in the septa of the gland and the wide lumina of intralobular ducts in the microscopic sections (Fig. 8).

With exacerbations and continued progression of this inflammatory process, infiltrating lymphocytic cells replace the parenchyma. Increasing fibrosis results in loss of acini, and myoepithelial cells line and tend to obliterate the lumina of the intralobular ducts. Some areas are less involved and these ducts continue to dilate and form cysts resulting in a cavitary appearances. In the advanced cases of Mikulicz's and Sjögren's diseases, reported by Castleman and Morgan[11,27] among others, the myoepithelial islands are scattered in areas of lymphocytic infiltration with fibrosis and absence of recognizable

Fig. 7.—A sialogram which demonstrates involvement of the submaxillary and parotid glands by non-obstructive sialodochiectasis in Sjögren's Syndrome. FILLING PHASE. The parotid gland architecture is bizarre and compatible with the destructive stage of Sjögren's Syndrome. The submaxillary sialectasis is of lesser degree.

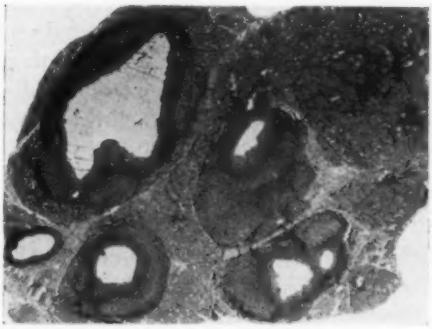

Fig. 8.—Pathologic correlation of non-obstructive salivary gland disease with sialograms. In the globular stage of sialectasis the sialographic finding of terminal duct dilation correlates with the wide lumens of the intralobular ducts on histologic section.

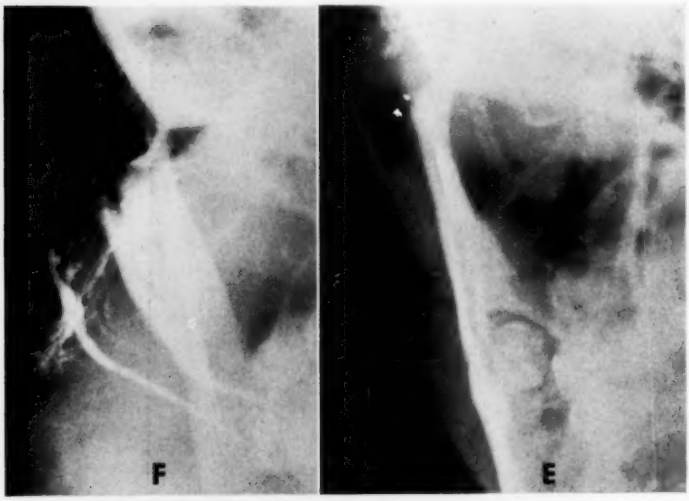

Fig. 9.—Sialography in tumors external to the salivary gland. In the FILLING PHASE there is a medial filling defect of the right parotid gland. The POST EVACUATION film indicates that the gland has emptied completely and is not involved.

ducts. It is interesting that Payne found a similar epithelial proliferation of the duct lining in the one biopsy specimen from a case of recurrent pyogenic parotitis. The authors do not feel that these changes are specific for Mikulicz's disease; they have encountered these findings in lymphoblastoma. In the end stages, the total absence of the glandular architecture and the atrophy of the parenchyma result from the diffuse lymphocytic infiltration and account for the bizarre and destructive pattern seen in the sialograms. Scattered areas of calcification are occasionally seen.

NEOPLASTIC DISEASE

Extrinsic Tumors. The first report of the use of sialography to determine whether the salivary glands contained neoplastic tissue was made by Kimm, Spies, and Wolfe.[28] The main criteria for ruling out glandular involvement rested on demarcation of the margin of the normal gland from that of the tumor. In many cases these authors did not distinguish external tumors from encapsulated intrinsic neoplasms in which the glandular architecture was preserved. This shortcoming in sialography was emphasized by Blady and Hocker,

who stated that the roentgen findings of benign mixed salivary gland tumors were simulated by benign growths, cysts, tuberculous adenitis, and lymph nodes with metastases.

Tumors external to the salivary glands are more often the cause of regional swelling about the angle and below the ramus of the mandible than are intrinsic salivary gland neoplasms. Metastatic adenopathy and lymphoblastomas are frequently seen as painless masses in the cervicofacial region. Tuberculous, syphilitic, and other infectious types of lymphadenitis are encountered less frequently and may be associated with a primary oral lesion. Tumors derived from the neighboring tissues, any of which may be a potential cause of swelling, are the problems in differential diagnosis. These include neurofibroma, lipoma, lymphangioma, chemodectoma, adamantinoma ,branchiogenic cyst, and aneurysm.

Scout films: Preliminary films occasionally make the diagnosis obvious, precluding the use of sialograms. Mandibular tumors and the characteristic "mulberry" calcification in a chain of tuberculous lymph nodes are readily identified.

Filling Phase: If the sialogram is normal, it indicates clearly that the cervical mass is external to the gland. More often the sialogram shows distortion of the duct structure from the adjacent tumor. The general architecture of the gland is preserved and there is only slight deviation of the intraglandular ducts, with no localizing narrowing, sharp kinking or bending. The filling defects are marginal and the bordering acinar pattern remains feathery (Fig. 9).

Emptying Phase: Secretory sialography is valuable in identifying extrinsic tumors, since complete emptying of the ducts and acini occurs immediately after stimulation. This is to be expected, since the parenchyma is displaced but intact and functioning normally (Fig. 9). This is one of the most valuable points in distinguishing extrinsic from intrinsic neoplasms, for in the latter lesions some retention of contrast material is usually evident in postevacuation films.

Intrinsic Tumors. It is apparent that it is impossible to determine the histologic type of any neoplastic process by means of sialography. Generally speaking, benign neoplasms are circumscribed or encapsulated and malignant tumors are infiltrative, but this is not always true. Encapsulation and invasiveness are distinguishable on sialograms and form the basis for reporting tumors of the salivary glands.

Some early reports of cancers of the salivary glands were based on clinical and roentgenographic findings, but many were not sub-

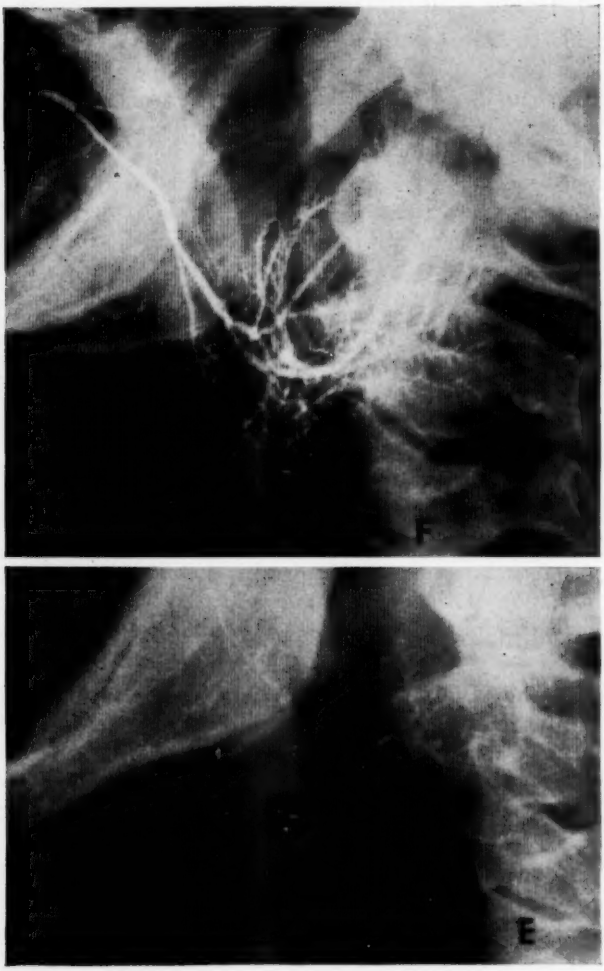

Fig. 10.—Sialogram of an intrinsic circumscribed or encapsulated tumor. The FILLING PHASE demonstrates a filling defect in the superior pole of the right parotid gland with displacement of the gland inferiorly. There is slight dilation of the distal portions of the interlobar ducts.

stantiated by histologic sections. Jacobovici, Poplitza, and Albu (1926)[29] reported two cases showing "deformity of ducts" but gave no pathologic findings. Barsky and Silberman[30] in 1952 stated that absence of duct markings in the region of tumor indicated a "malignant character of the tumor" but failed to report the microscopic findings in three of the six cases documented. Czillag and Czunft[31] in 1934 said, "Cancer of the parotid gland can be recognized by the destruction of the finer ramifications of the excretory ducts and by filling defects due to the destruction of the glandular substance." The most accurate and complete analysis of salivary gland tumors was made by Blady and Hocker[32] in 1937. They reported clinical, roentgenographic, and pathologic observations in 76 tumors of the salivary glands, 24 of which were malignant, and established the diagnostic criteria now generally accepted. The changes noted were present in only 62 per cent of their cases of primary carcinoma of the salivary glands. The reason for the failure to demonstrate the changes may be due to the fact that when carcinomatous processes occur in encapsulated lesions, no evidence of infiltration is present.

Scout Films: Screening films as a rule are not very helpful. In rare instances an amorphous collection of calcification in a soft tissue mass may suggest calcifying cartilaginous tissue in a mixed salivary gland neoplasm. When there is destruction of the mandible, it is usually due to neoplastic disease arising in this bone.

Filling Phase: The most consistent roentgen finding of an encapsulated or circumscribed intrinsic lesion is a filling defect outlined by a displaced duct system (Fig. 10). The general architectural pattern of the duct system is preserved; each duct is seen in its entirely, although its shape and configuration will vary with its degree of displacement. The position and size of the tumor determine the sialographic findings. Centrally situated masses result in wide separation of the larger adjacent subsidiary intraglandular ducts. If the tumor is located peripherally, the displacement of the terminal arborizations may simulate an extrinsic mass. The main duct is more sharply angulated by the pressure of masses in the anterior portion of the gland.

Circumscribed masses may be solid or fluid-filled cysts, both presenting clinical and radiographic problems in differential diagnosis. On clinical examination, the cyst is usually outlined as a smooth, symmetrical structure; whereas a solid neoplasm is characteristicaly hard and nodular. Radiographically, the ducts surrounding a cyst are stretched and thinned in a diffuse manner by the cyst as seen on the sialogram (Fig. 11).

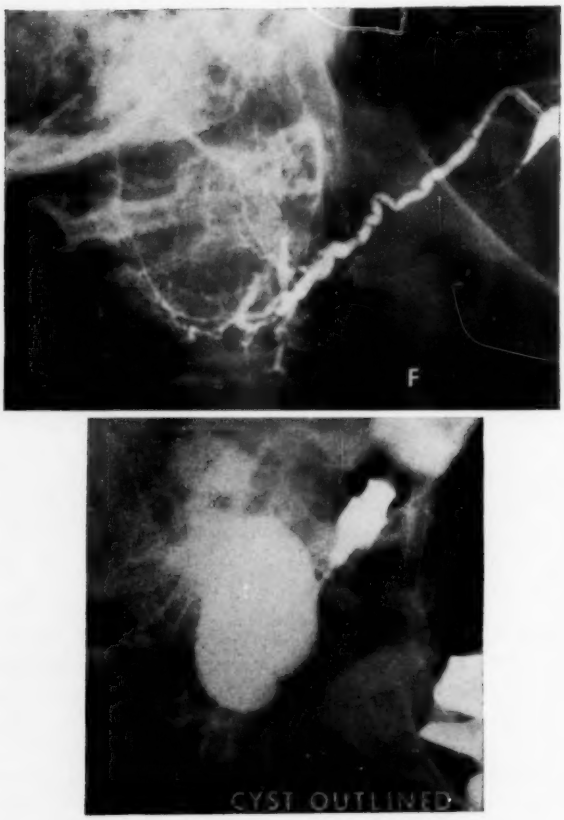

Fig. 11.—Sialogram of an intrinsice encapsulated inflammatory cyst. The FILLING PHASE shows tortuosity and dilation of Stenson's duct compatible with simple duct obstruction. A space occupying mass in the postermedial portion of the gland displaces the secondary and tertiary ducts. The duct system is intact. Aspiration of 17 ml of fluid followed by injection of an equivalent amount of 30 per cent Urokon® to outline the cavity of the cyst.

Malignant neoplasms are generally infiltrative in type. The architecture of the gland is disrupted and the degree of sialographic abnormality depends on the extent of involvement. The duct system is displaced and distorted by the expanding neoplasm. The acinar pattern is replaced by a bizarre puddling and pooling of the radiopaque media, since the terminal ducts are destroyed by neoplastic invasion and the injected contrast material escapes into the adjacent tissues (Fig. 12).

Emptying Phase: Following reflex stimulation of the salivary glands that have circumscribed or encapsulated neoplasms, some retention of contrast material is noted. The normal gland tissue is compressed between the slowly growing tumor and the capsule of the gland. This results in patterns characterized by some evidence of segmental intraglandular duct retention (Fig. 10). Intrinsic invasive neoplasms, however, show virtually complete retention of the contrast material because of the loss of secretory function secondary to replacement of normal gland parenchyma by neoplasm (Fig. 12). It should be reiterated that these bizarre puddling and pooling patterns are indistinguishable from the radiographic picture of destructive sialectasis (Fig. 7). The differential point lies in the fact that other major salivary glands, exclusive of the one involved by a tumor, show the normal sialographic pattern.

It should be stressed that the terms "encapsulated or circumscribed" and "invasive" are not synonymous with "benign" or "malignant"; no attempt should be made to diagnose the histologic type of salivary gland neoplasm on the basis of sialographic evidence.

SUMMARY AND CONCLUSIONS

According to certain clinical, pathological, and sialographic criteria, inflammatory diseases of the salivary glands may be classified as:

1. Chronic obstructive sialodochiectasis, in which the abnormalities are primarily in the main duct. In this group, calculi and strictures are the principal entities. As shown roentgenographically and histologically, the ducts that are dilated are the main duct and the interlobar and interlobular septal channels.

2. Chronic nonobstructive sialodochiectasis, or sialectasis, in which the abnormalities are principally in the peripheral ducts. This group is composed of heterogeneous but clinicaly related diseases which have a similar and characteristic pattern of sialectasis. These entities include Mikulicz's disease, Sjögren's syndrome, and recurrent pyogenic parotitis in adults and children. By studying the filling and emptying phases of secretory sialography, the altered anatomicophysio-

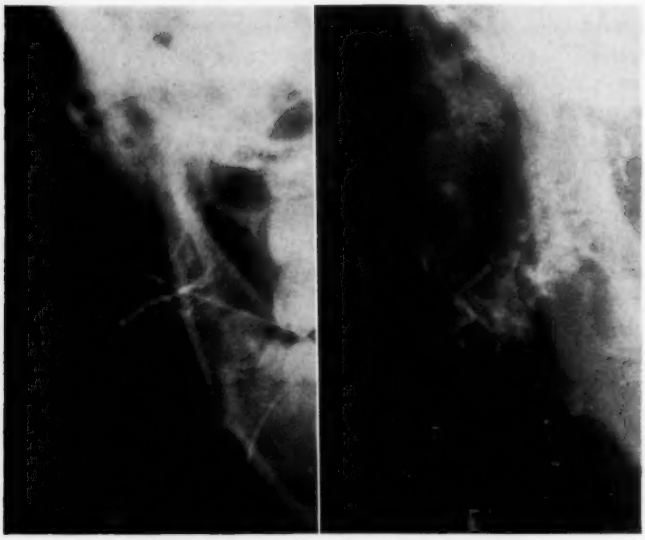

Fig. 12.—Sialogram of an intrinsic invasive tumor of the parotid gland. The FILLING PHASE demonstrates a large mass in the right parotid gland displacing and altering the duct architecture. Following stimulation, the contrast material appears to have permeated the surrounding acinar tissue instead of being evacuated from the gland. Histologic diagnosis: Hemangio-endothelial sarcoma of parotid gland.

logic pattern of sialectasis may be identified and classified into four stages:

1. Punctate (early stage)
2. Globular (moderately advanced stage)
3. Cavitary (advanced stage)
4. Destructive (end stage)

The histologic changes of nonobstructive sialodochiectasis common to the diseases mentioned correlate with and confirm the roentgen pattern of sparse, stenotic, interlobar and interlobular ducts and dilated intralobular ducts.

Secretory sialography is valuable in identifying tumors extrinsic to the salivary glands, for when tumors are present the complete emptying of the duct system occurs immediately following stimulation of the glands. Intrinsic salivary gland neoplasms, however, show retention of contrast material in postevacuation films.

TABLE I

NUMBER AND TYPE OF CASES
JULY 1953 - FEBRUARY 1956

I.	Normal			40
II.	Inflammatory:			
	A.	Chronic Obstructive Sialodochiectasis		26
		1. Calculi	20	
		2. Strictures	6	
	B.	Chronic Non-Obstructive Sialodochiectasis		30
		1. Recurrent sialadenitis in children	7	
		2. Recurrent pyogenic parotitis	4	
		3. Sjögren's Syndrome	14	
		4. Mikulicz's Disease	5	
III.	Neoplastic:			
	A.	Extrinsic tumors		13
	B.	Intrinsic tumors		26
		1. Encapsulated or circumscribed	20	
		2. Cystic, Inflammatory	2	
		3. Invasive	4	
	TOTAL			135

Neoplasms of the salivary gland can be shown to be circumscribed (encapsulated) or invasive, but their histologic type cannot be identified by sialographic techniques. The most consistent roentgen finding in circumscribed or encapsulated intrinsic neoplasms is a filling defect outlined by a displaced duct system. The general architectural pattern of the duct system is preserved. Retention of contrast material in postevacuation films is characterized by segmental intraglandular duct retention with differences due to the anatomical location and size of the tumor.

Infiltrative neoplasms characteristically show disruption of the gland architecture in the filling phase. The secretory phase shows retention of the contrast material where the acinar pattern is replaced by a bizarre puddling and pooling of the radiopaque material. Comparison with the histologic changes indicates that retention results because the normal acinar tissue has been destroyed or replaced by invasive neoplasm and the secretory function is lost.

Although sialography is not a new procedure, the recently developed modification termed "secretory sialography" has enhanced its value as a diagnostic and interpretive aid.

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XXVI

THE CORTICOSTEROIDS IN OTOLARYNGOLOGY

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The recent era of antibiotics and other antimicrobial agents has encouraged us to think mostly about destroying invading organisms and to *forget about the host.*[34] With more knowledge and use of the hormones, it becomes necessary for us to direct our thoughts to the natural protective mechanisms of the body. The corticosteroids may be harmful to individuals with certain pathologic conditions; also overdosage is temporarily harmful to all. Therefore, it behooves us, when possible, to use these agents in conditions and in doses that will not harm the tissues and functions of the body. If this is done, we will find that we now have some very useful tools which were not at our disposal only a few years ago.

In order to prevent repetition, the terms corticosteroids, corticoids, and glucocorticoids will be used interchangeably and designate the 11-oxycorticoids, or cortisone-like hormones.

If one reviews the literature on the pituitary and adrenal cortical hormones, one will become somewhat dizzy on finding the stupendous amount of investigative work being done on this subject. Also, one will be astounded to find that these hormones can effect almost any physiologic and pathologic condition in the body. Other noticeable things in this review will be that, in most of the investigative work, the hormonal doses used are very large and often the results were contradictory. To add to the confusion, presentations of hypotheses explaining, or trying to explain, the mechanism of actions of the corticoids are innumerable.

The literature reveals that there is even some question about the number of hormones produced. For example, Li[1] believes there may be more than one ACTH. Verzar[2] gives evidence that, normally, mineralo-corticoids are not secreted by the adrenal cortex, but are only intermediate products which eventually are metabolized to glucocorticoids. He explains the mineralo-activity, as well as the protein and fat action on the gluconeogenesis produced by the 11-oxycorti-

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coids. He states that only the 11-oxycorticoids can be found in the blood stream. Godlowski[3] presents the hypothesis that the corticosteroids ameliorate allergic symptoms by improving the inefficient proteolytic enzyme systems so that the foreign proteins are more readily broken down to their normal end products. In spite of all the confusion, there is one observation that stands out, i.e., the diseases which respond best to the corticoids are those in which some allergic phenomenon operates and where there is involvement of the connective tissue.

The main function of the pituitary-adrenal axis is the maintenance of healthy cells and tissue, not only under normal physiologic conditions, but also under stress.[4] Hence, any human who does not possess an efficient mechanism for the production of cortical hormones is basically ill.

There are a few direct effects of ACTH which follow without the intervention of the adrenal cortical steroids. The most important of these are the ascorbic acid depletion of the adrenal cortex, weight maintenance of the cortex and hypertrophy of the cortex.[1] The other innumerable actions involved in the pituitary-adrenal function of maintaining homeostasis, are produced directly or indirectly by the cortical hormones themselves. Some of these actions, along with a few negative findings, will now be related.

ACTIONS RESULTING FROM THE USE OF 11-OXYCORTICOIDS

1. Produces eosinopenia.[5]

2. Produces lymphopenia.[5]

3. Produces involution or breaking down of lymphatic tissue.[5] (This breaking down of lymphocytes can liberate antibodies preformed in the lymphatic tissues. Also, the destruction of lymphatic tissue can depress the synthesis of antibodies.)

4. Produces generalized leukocytosis but inhibits the migration of neutrophils to a local inflammatory area.[5]

5. Produces gluconeogenesis.[2] (i.e., making glucose available even if it has to be produced from protein or fat.)

6. Has anti-inflammatory and antiphlogistic action[5] with depression of all elements of granulation tissue.[6,7]

7. Has antitoxic action.[5]

8. Has antihyaluronidase activity in vivo.[8]

9. Inhibits formation of hyaluronic acid of the ground substance.[7,15] (i.e., decreases the amount of ground substance.)

10. Inhibits the Shwartzman phenomenon[9] as well as the tuberculin reactions.[10,12]

11. Inhibits reactivity of the conjunctivae and nasal mucosa to the antigen antibody reaction.[10]

12. Inhibits increased capillary permeability produced by hyaluronidase in all inflammatory reactions studied.[11] (This increased capillary permeability produced by the spreading factor is probably due to liquefaction of the ground substance around the capillaries. The corticoid action in inhibiting this phenomena may be due to antihyaluronidase activity.)

13. Inhibits production of inflammatory edema.[5]

14. Increases excretion of uric acid.[14]

15. Increases amplitude of skeletal muscle contraction.[16]

16. Increases coagulability of the blood (increasing the possibility of thrombo-embolic complications).[17]

17. Fails to effect the release of histamine into the blood stream in the antigen antibody reaction.[18]

18. Fails to block histamine.[18]

19. Fails to affect the histamine or allergic skin tests.[18]

20. Fails to affect the antibody production in humans, except in very large and prolonged dosage.[19-21]

21. Raises the blood level of nonspecific hyaluronidase inhibitor in normals, but lowers it in cases of rheumatic fever and arthritis who have been successfully treated with corticosteroids.[22] (i.e., the pituitary adrenal axis regulates the amount of non-specific hyaluronidase inhibitor found in the blood stream.)

22. Decreases the permeability of ground substance.[23] (This is tremendously important since the consistency of the ground substance regulates the passage of substances from the parenchymatous cells to the circulation and also the passage of organisms from the surface, which are trying to penetrate to the blood stream and other deeper vital structures. No blood vessels directly supply any cells. All vascular substances must penetrate the ground substance before reaching any cell.)

23. Helps maintain a good peripheral vascular bed[24,25] (by improving smooth muscle tone and maintaining healthy capillary endothelium).

24. Degranulates the connective tissue mast cells, thus liberating a heparin-like substance.[26]

25. Depresses the activity of mesenchymal wandering cells.[37]

26. Aids nerve tissue to synthesize acetylcholine.[16]

27. Aids control of the metabolism of histamine.[27] (The histamine content of blod and tissues being increased in adrenalectomized animals.)

28. In large doses lowers the host's resistance to infection and enhances it in small doses.[28-32]

29. Protects single cells from degeneration.[33]

Some of the above actions are very important in otorhinolaryngology and require elaboration.

INFLAMMATION AND CORTICOSTEROIDS

Inflammation can be produced by any stress, and is a chain reaction set off and continued by substances released through cell damage.[13] Damaged cells are mainly fibroblasts. The severity of inflammation depends upon the inflaming stimulus and the amount of hormones available.[13] It is a definite and well accepted fact that the corticoids have marked anti-inflammatory action and that growth hormone and thyrotropic hormone enhance inflammation.

Dougherty[13] gives the following hypotheses as to possible mechanisms in anti-inflammatory corticoid action:

1. Decrease in the level of circulating fibrinogen, thus producing a decrease in the amount of fibrin at the site of inflammation.

2. Inhibition of hyaluronidase, thus decreasing the action of the spreading factor.

3. Inhibition of the formation of hyaluronic acid of the ground substance.

4. Shedding of mast cell granules with release of a heparin-like mucopolysaccharide which has antihyaluronidase action and which also binds histamine.

To this list could be added the action of maintaining a good capillary bed. Dougherty believes that all of these actions take place but that there may be a more fundamental anti-inflammatory phenomenon involving the action of hormones on the many substances liberated through cell damage.

INFECTION AND CORTICOSTEROIDS

There is no question but that the glucocorticoids in large doses impair the host's resistance to many infections. There are numerous

explanations for this. Thomas[32] states that there are at least six possibilities. They are as follows:

1. A direct effect on the infecting organism. There is no direct evidence that this takes place.

2. An effect on the neutrophils. Although cortisone produces a systemic leukocytosis, fewer pus cells migrate to the area of local inflammation. There is slight evidence, but no definite proof, that the bactericidal properties of leukocytes are diminished. Some virus infections are also enhanced by large doses of corticoids and since available evidence shows that neutrophils are not important in virus infections, the leukocyte hypothesis becomes somewhat untenable.

3. Influence in antibody formation. There is no definite evidence that this is a factor in humans.

4. Interference with the inflammatory reaction. The corticoid depression of tissue inflammation is an accepted fact, but, as noted above, the explanation is uncertain. At any rate, the anti-inflammatory theory does not explain the enhancement of virus infections, nor the enhancement of bacteria which are injected directly into the blood stream. In these two instances, there is no local inflammatory reaction. Of course, some cellular component present in the blood stream could be involved and the hormone could work on it here.

5. The effect on serological mechanisms, such as the nonspecific hyaluronidase inhibitor.

6. Damage to the reticuloendothelial system. The macrophages in this system are for the purpose of clearing the blood stream of bacteria and particulate matter. There is some evidence that like certain colloids, cortisone blocks the cells of the reticuloendothelial system so that the macrophages then cannot clear the blood stream of infectious organisms.

It can readily be seen that the phenomenon whereby large doses of corticoids enhance infection, is not easily explained by any one hypothesis.

On the other side of the picture, Robinson and Smith,[29] Vollmer[30] and Lurie[31] give evidence to show that in small doses, these hormones not only fail to enhance infection, but aid the infected host and protect the host from infection. Also, Robinson and Smith state that, to date, many patients have received cortisone and the number of reports citing intercurrent infection, has been negligible.

Jawetz[34] states that in patients seriously ill with infection and toxemia, the antitoxic effect of cortisone may save the patient while a proper antibiotic is destroying the infection.

It would appear that, as far as infection is concerned, with doses of corticoids large enough to produce symptoms of hyperadrenocorticoidism, there is enhancement of the infection, and that with very small doses there may be improvement of the host with inhibition of the infection.

POOR STRESS MECHANISMS AND THE CORTICOSTEROIDS

It is my belief, that at the present time, we do not have any test that is sensitive enough to determine mild cases of hypoactivity of the pituitary adrenal axis. For example: Sternberg and Zimmerman[36] made Thorne tests on a group of allergic patients and they all showed a normal lowering of the eosinophils. These patients received a severe stress test and none of them responded normally. Their stress mechanisms were all under par. They all responded well to cortisone. This would indicate that many patients have a mild undiagnosed hypoactivity of the pituitary adrenal axis. In our specialty, this group of patients would include those who fatigue easily and are susceptible to upper respiratory infections, and, in general, those who have the symptoms of chronic physical allergy. It is not beyond the realms of possibility that in the future, some of these cases will be successfully treated and maintained on very small doses of corticoids just as mild hypothyroids are maintained on small doses of thyroid. I sincerely believe that this line of approach deserves further consideration and investigation.

THE MAST CELL AND THE CORTICOSTEROIDS

Recently, the mast cell has taken on considerable significance in the investigative work on the corticoids. The mast cell, with basophilic staining, is a granulated, mesenchymal cell.[35] The granules contain a heparin-like substance, which is a mucopolysaccharide and apparently an inhibitor of hyaluronidase.[20,38,40]

Tissues rich in mast cells and heparin, contain much hyaluronidase inhibitor and other tissues do not.[39]

Lick and Sylvan[40] give evidence that the mucopolysaccharide in mast cells is the nonspecific hyaluronidase inhibitor.

Stuart[41] has found that shock organs of different species contain large amounts of mast cells, and he believes that these cells are important in the defense mechanisms in anaphylactic shock.

Bensley[35] produced a great increase in mast cells by injecting histamine into the skin.

Zweifach[42] states that mast cells release their granules when the organism is under stress and he also states that they are usually found in large numbers around blood vessels.

The work of Asboe-Hansen[39] indicates that thyrotropic hormone increases the mast cells in connective tissue and also makes them become more granulated, while cortisone decreases the number of these cells, degranulates them and decreases the amount of ground substance. He believes that the mast cells transmit this corticoid action of decreasing the ground substance.

The above investigations indicate that one of the important functions of the mast cell is the maintenance of good ground substance and that the corticoids control this action. The mucosa of the nose and sinuses contain many mast cells.

EDEMA, CAPILLARY PERMEABILITY AND THE CORTICOSTEROIDS

In the practice of otorhinolaryngology, edema is often one of our worst enemies and, hence, I will briefly consider this subject in connection with the corticoids.

Burton[43] gives a new concept on the nature of arteriolar or precapillary spasm. He found that when the pressure within the capillaries falls below a certain critical valve (this depends on the capillary size, firmness of the surrounding tissue and vasomotor tone) that they collapse suddenly and completely. It is not a gradual process. At pressures above this critical level, the capillaries act like rigid tubes. This phenomenon favors Williams'[48] hypothesis of arteriolar spasms in conditions such as histamine cephalalgia, Ménière's disease and Bell's palsy. In all of these conditions, the symptoms come on very rapidly.

Papenheimer[44] found that the interendothelial cement substance makes up only about .2 per cent of the available endothelial capillary surface and this small area was entirely inadequate to account for the observed rate of transfer of oxygen and carbon dioxide across the capillary wall. He suggested that oxygen and carbon dioxide and other lipid soluble substances diffuse mainly through the endothelial cells themselves.

Renkin[45] experiments bear this out. Hence, since the corticoids aid in maintaining healthy capillary endothelial cells, they may aid in providing oxygen and nourishment to the finer structures in our specialty.

Zweifach[42] suggests that capillary permeability not only depends on the endothelial lining, but also upon all five elements of the hematoparenchymal barrier. These elements are the proteinaceous covering over the endothelial cells of the capillaries, the endothelial cells themselves, the interendothelial cement, the pericapillary sheath and the ground substance of the connective tissue. None of these structures are inert, but all are in a constant state of metabolic flux and, hence, vary from time to time. Therefore, the permeability of each structure varies from time to time and, hence, the importance of this effect on edema.

Zweifach thinks that the firmness of the pericapillary sheath is of the utmost importance in preventing edema and Seifer[46] states that the ground substance with its pericapillary sheath, surrounding these vessels, exerts the ultimate control of capillary permeability.

The above observations indicate that we can no longer accept Starling's[47] hypothesis (hydrostatic forces vs. osmotic forces) as the sole factor in capillary permeability and that the production of edema is not only a matter of arteriolar spasm, but is of a very complex nature.

The importance of the corticoids in preventing edema takes on great importance because of their action in maintaining the integrity of the capillary endothelial cells and especially in decreasing the permeability of the ground substance and its pericapillary sheath which surrounds the capillaries.

From the foregoing observations and comments, it becomes obvious that the last word has not been written about the mechanisms of action of the corticosteroids. It is my feeling and belief that more definite information will be forthcoming only when we know more about tissue and cellular enzyme activity. At the present time, the watch word in using these hormones is "caution." However, I do believe that with care, careful study and close observation of patients, there are several of the ear, nose and throat conditions in which the use of the corticosteroids is indicated.

GENERAL ASPECTS AS RELATED TO OTOLARYNGOLOGY

The contraindications for the use of corticosteroids are so well known that they will not be commented upon except to say that they naturally apply in otolaryngology just as in any other field.

A low salt diet is advisable. High protein diet with the addition of potassium is usually not necessary unless rather prolonged treatment with reasonably high dosage is used. During corticosteroid

therapy, an occasional injection of ACTH is indicated in order to stimulate the adrenal cortex. Gradual corticoid withdrawal is usually not necessary except with fairly high and prolonged dosage. Intravenous ACTH gives the maximum stimulation of the adrenal cortex. When infection is involved, the appropriate antibiotic should be used. Wound healing is not stopped but merely inhibited by the corticosteroids. For local use, hydrocortisone is the hormone of choice.

The use of these hormones in large doses over long periods should not be recommended in most otolaryngological conditions. One of the most serious problems in corticosteroid prolonged high dosage therapy, is the depression of the adrenal cortex. If we eliminate this kind of therapy, we greatly reduce this danger. However, in surgical cases, if there is any possibility of cortical depression from previous therapy, prophylactic corticoids should be given before and for a few days following surgical stress. Also, intravenous hydrocortisone and intravenous ACTH should be available for emergencies.

The author has had only a small experience with the newer glucocorticoids, meticorten and meticortelone. These synthetic hormones are very powerful but they have very slight mineralo-activity. If time shows that other side reactions are of minimum degree, they should be very useful. They should be of particular value when used in conditions where the main problem is one of edema.

OTOLARYNGOLOGIC CONDITIONS IN WHICH THE CORTICOSTEROIDS ARE USEFUL

1. *Hay fever.* Particularly in severe cases not controlled by ordinary methods and in localities where the season is short. Besides systemic therapy the local use of hydrocortisone eye drops is effective. The local use of hydrocortisone intranasally is only mildly effective.

2. *Status asthmaticus.* In this serious condition, intravenous hydrocortisone or intravenous corticotropin may be a life saving procedure.

3. *Penicillin and other drug reactions, hives and angioneurotic edema.* These maladies are usually self-limited and respond well to the corticosteroids.

4. *Acute edema of the larynx.* Whether the edema is from infection or trauma, the use of the corticoids may prevent the necessity of doing a tracheotomy.

5. *Critically ill and toxic patients.* The corticosteroids can tide the patient over while antibiotics and other supporting measures are carried out.

6. *Idiopathic midline granuloma of the facial tissues.* ACTH and the corticosteroids are the most effective treatment in this serious condition.

7. *Erythema multiforme.* In many such cases, lesions in the mouth are the first sign of this disease. Hence, the otolaryngologist may be the first to see the patient or may be called in consultation. Corticosteroids with appropriate antibiotic therapy give relief and shorten the course of the disease.

8. *Pemphigus.* Like erythema multiforme, the first signs of pemphigus are often lesions in the mouth. Until the era of corticosteroids and corticotropin, this disease has been considered to have a fatal outcome. The author has been consulted in three cases of pemphigus. All were treated with corticotropin, corticosteroids and antibiotics. Two are now well on no therapy and one is free of symptoms on a maintenance dose of hydrocortisone.

9. *Histamine cephalalgia.* If histamine and other vasodilating types of therapy fail to give relief, corticosteroids, and particularly intravenous corticotropin, will often bring about improvement. However, vasodilating therapy should be continued.

10. *Contact ulcer of the larynx.* Cauterization or fulguration of the lesion followed by a short course of corticosteroid therapy is well justified in this condition. Granulation tissue is diminished and epithelium can more readily cover the ulcer.

11. *Laryngeal polyps and extensive nasal polyps.* The following regime is recommended in these conditions:

a. Surgical removal of the polyps.
b. A short course of postoperative corticosteroid therapy.
c. Elimination of etiological factors.
d. Appropriate allergic treatment.

12. *Fresh stricture of the esophagus.* Less scarring results if the corticosteroid therapy is initiated immediately. Standard treatment should also be followed.

13. *Eczema and dermatitis of the external canal.* Local use of hydrocortisone with the appropriate antibiotic is very effective in these cases.

14. *Bell's palsy.* In early cases of Bell's palsy, we have had very good results with the use of vasodilators combined with corticosteroids and a low salt diet.

15. *Ménière's disease.* We are now treating Ménière's disease in a manner similar to that of Bell's palsy. That is, a combination of vasodilatation, corticosteroids and low salt diet. The author's experience is not large enough to accurately comment upon the effectiveness of this form of treatment in Ménière's disease.

16. *Preoperatively and postoperatively in patients with depressed adrenal cortices.* This has already been discussed.

17. *Local spray and mist hydrocortisone therapy in respiratory allergy.* We have had only moderate success with this local type of therapy.

18. *Postsurgical edema.* In surgical cases where postoperative edema is often a problem, corticosteroids can be effectively used. The author has found these hormones especially useful following nasal reconstructive surgery.

19. *Status lymphaticus.* This condition is supposedly due to a hypoactivity of the adrenal cortices and may result in death from very mild stress. Death from anesthesia furnishes the most typical example. If intravenous hydrocortisone could be administered early enough, recovery could be anticipated.

20. *Anaphylactic and other forms of shock.* Intravenous hydrocortisone is one of the most effective measures.

21. *Emergency surgery in debilitated patients.* When it becomes necessary to do surgery in debilitated patients, stress hormones should be administered just before and a few days following surgery.

22. *Patients with a poor stress mechanism.* It has been apparent to the author that there is a large group of patients afflicted with a poor stress mechanism. Although we have not done any stress tests, it would appear that this group would include patients who have some or all of the following symptoms and findings:

a. Tire easily and always feel under par.

b. Low body temperature.

c. Cannot tolerate dampness, drafts and sudden changes in weather.

d. Are easily upset by emotional stress.

e. Often have symptoms of chronic perennial allergy.

f. Are much better in a warm, dry climate without sudden changes.

g. Are very susceptible to mild virus upper respiratory infections. (In this regard, these patients usually state that they will develop a sore throat and stuffy nose if in a draft, if in an air-conditioned room, if they wash their hair and go out in the cold air, or if they encounter any similar mild stress.)

If I am not mistaken, your offices are crowded with this type of patient. I believe that intermittent low dosage corticosteroid therapy would aid these patients and also, in so doing, there would be no depression of the adrenal cortex. A suggested dose would be one to two milligrams of hydrocortisone twice daily. Experience alone will determine whether or not this type of treatment for this type of patient is effective and worthwhile.

SUMMARY

Some of the actions of the corticosteroids have been noted and mechanisms of actions have been discussed. Comments, in some detail, have been given on the relationship between the corticosteroids and inflammation, infection, stress, mast cells and edema. Practical aspects in relation to otolaryngology have been considered. Specific otolaryngological conditions have been cited where the corticosteroids are useful. Emphasis has been placed on the possible effectiveness of low dosage maintenance therapy in patients with a poor stress mechanism.

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XXVII

EXTENSIVE VENOUS OBSTRUCTION OF THE LABYRINTH

A. COCHLEAR CHANGES

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Vascular lesions of the labyrinth have been under investigation in this laboratory for the past four years. The effect of obstruction of the inferior cochlear vein was reported on in 1952.[1] Only minimal histological change and no functional change as tested electrically was found. Further studies have been made possible by development of a method for direct observation of the vessels in the stria vascularis and spiral ligament through the microscope and recording by means of the motion picture camera.

A series of direct observations on the circulation following this procedure in the living guinea pig have been recently described by us.[2,3] As stated in one of these reports the effect of interruption of the inferior cochlear vein has been found to depend upon the location of the obstruction with relation to collateral vessels. Obstruction of the vein along with its collaterals has been found to produce an immediate reduction of blood flow in the strial capillaries. Preliminary functional tests (microphonic and action potentials) indicate a profound loss of auditory function.

In order to determine the histopathologic changes produced by interruption of the venous return in this manner a series of acute and chronic experiments have been carried out.

The purpose of this report is to present primarily the histopathologic changes which occur at various time intervals following obstruction.

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MATERIALS AND METHODS

A total of fifty guinea pigs weighing from 200 to 450 grams were used for the entire experiment. Thirty-eight of these were used for histologic study of the chronic conditions, the remainder to study acute changes in circulation. The anesthetic used was veterinary nembutal, intraperitoneally 0.5 cc for each kilogram of the body weight. As previously reported the guinea pig is particularly suited for this investigation because the inferior cochlear vein runs in a bony canal entirely separated from the cochlear aqueduct, as in the human, and is surgically accessible.

The operations in these chronic experiments were performed under sterile conditions with a microscope (15X). The styloid process was cracked at its base and retracted medially. The mandible was not cracked. The bulla was opened posteriorly without traumatizing the tympanic membrane. The inferior cochlear vein was exposed almost in its entire length with its collaterals, removing the superficial bone with a fine burr (0.5 mm). These vessels were then obstructed widely to reduce reanastomosis; the drilling was stopped at the junction of the cochlear vein and vestibular veins. Irrigation with normal saline was used to prevent heating and the operated area was packed with bone dust and bone wax. The inner ears were not entered. One ear was operated upon in each animal, the other ear remaining as a control.

The time of sacrifice was as follows: one, three, six, twelve hours; one, two, three, five, six, seven, fourteen days; one, two, three, five, six months with one or more animals in each group. The majority of animals were perfused under the same conditions in temperature (38° C), volume of normal saline (40-50 cc), of Heidenhain-Susa solution (130-150 cc) and pressure (30″ H_2O). One animal died and seven were decapitated for a specific purpose to be described later. In all specimens the ears were kept intact with midbrain and cerebellum. The bulla cavities were opened, and the block of tissue fixed one day, decalcified for three days and passed through the standard process for the temporal bone celloidin technique which requires two months to prepare for cutting. All specimens were cut horizontally at 18 microns reaching the spiral ligament of the ventral basal turns of both cochleae simultaneously so that histology could be compared on both sides in the same region (Fig. 1). Every fifth section was stained with H and E. Sixteen linear charts were made from the spiral graphic reconstruction of the cochleas after the method of Guild[4] to illustrate the pathologic changes.

Fig. 1.—Section through both labyrinths and brain stem permitting comparison of the pathological ear with the opposite normal control.

FINDINGS

Cochlear Circulation. Blood flow rate in the strial capillaries is immediately and markedly (90 per cent) reduced after obstruction of the inferior cochlear vein and its collaterals. Change of flow in the other vessels (arteriovenous arcade and arteriole) is less marked. Vasomotion was not observed in any of these vessels following obstruction.

In the chronic experiments reported here direct observations on the circulation in the cochlea could not be made since the inner ears were not opened.

Symptoms. When the animals recovered from the anesthetic they showed varying degrees of vestibular disturbance consisting of horizontal nystagmus toward the unoperated ear, tilting and turning of the head toward the operated ear and circling movements toward the operated side. A preliminary investigation of the cochlear microphonic and action potential responses following such a lesion showed a severe loss.

Histopathology. Blood Vessels. In all 38 animals with chronic changes the inferior cochlear veins were completely obstructed, and collaterals and vestibular veins to various degrees. Frequently the

obstructed vessels anastomosed with the vessels of the middle ear, but not with the distal ends of the obstructed inferior cochlear veins. The diameter of the cochlear vein at the second and third turn was markedly reduced in some specimens. At the junction of the cochlear and vestibular veins fibrosis and ossification of their bony canals often markedly reduced the diameter of these veins. The vessels along the endolymphatic duct and sac were often seen to be dilated. The coiled arteries in the modiolus sometimes were occluded (Fig. 2). Increased vascular anastomoses were not demonstrable between the vena spiralis posterior and the veins of the modiolus or between the vessels of the otic capsule and that of the membranous labyrinth.

Hair Cells. Loss of outer hair cells was clearly observed 24 hours after vascular obstruction. The extent of outer hair cell damage after 24 hours in 33 animals was as follows: Basal turn only, 37 per cent; isolated lesions scattered throughout the cochlea, 24 per cent; continuous lesions from base to apex, 21 per cent; no lesion, 18 per cent. The degree of hair cell damage varied within the same period from no visible change to complete degeneration. Damage in the basal turn was found in all animals showing sensory cell changes. Continuous loss throughout the cochlea was first seen after two weeks of venous obstruction.

Loss of inner hair cells were first seen in a specimen two days after obstruction. The lesion was small, sporadic and located in the ear where outer hair cells were degenerated (Fig. 3).

Spiral Ganglion. Loss of ganglion cells was first seen two weeks after obstruction. The most extensive loss was seen after five months. The loss of ganglion cells was generally scattered and the largest loss measured in any one field was 80 per cent (Fig. 4). Complete degeneration of the spiral ganglion throughout the cochlea was not observed even when the outer hair cells were completely degenerated.

Stria Vascularis. The stria vascularis was extremely vulnerable and showed the first signs of damage. The location and extent of the change varied even in lesions of the same duration. Lesions at the basal turn were most common.

Dilatation of capillaries and edema of the epithelium was noted one hour after venous obstruction. Within a few hours hemorrhage into the epithelium and into the scala media was seen. Pallor and atrophy followed by disintegration of the epithelial layer occurred in the early hours after obstruction. After one week the histologic lesion of the stria vascularis was more marked as shown by the following changes: a. hypertrophic epithelium with highly dilated capillaries; b. partially denuded epithelium at the area close to the spiral

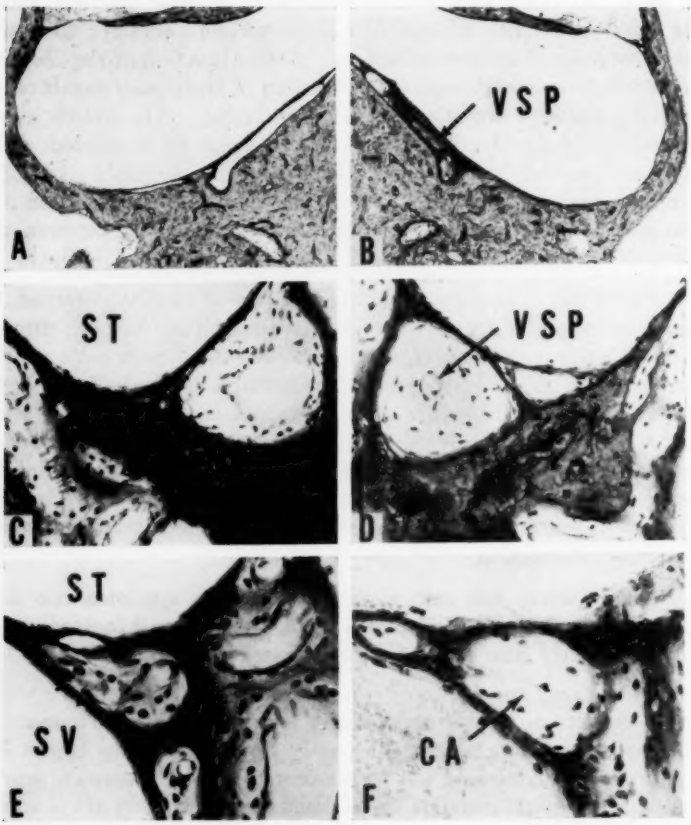

Fig. 2.—Blood vessel changes.

A. Normal venous channel in region of obstruction.

B. Corresponding venous channel two months after surgical obstruction.

C. Normal venous channel second turn of cochlea.

D. Narrowed venous channel two months after obstruction, corresponding level.

E. Normal coiled arteries, third turn of cochlea.

F. Obliterated arteries one month after venous obstruction, corresponding level.

V.S.P. Vena spiralis posterior
C.A. Coiled arteries of modiolus
S.T. Scala tympani
S.V. Scala vestibuli.

prominence; c. flat atrophic epithelium with marked reduction in number of capillaries; d. a simple cuboidal epithelium without capillaries (Figs. 5 and 6). In five animals almost complete strial degeneration was seen after two weeks of venous obstruction. The endothelial cells of strial capillaries sometimes appeared to be phagocytic.

Spiral Ligament. The earliest change was seen in a specimen of six hours in which the nuclei of the cells of the spiral ligament adjacent to the cells of Claudius and external sulcus cells showed pyknosis. This area became acellular and was occupied by a pink staining amorphous ground substance at two weeks. The degeneration was limited to the area below the spiral prominence when the lesion was small (Fig. 7B), but extended behind the stria when the stria was severely degenerated and the coiled arteries at the modiolus were occluded (Figs. 6 and 5H). The degeneration continued throughout the cochlea but the basal turn was especially vulnerable. New bone formation was observed within the atrophic spiral ligament adjacent to the otic capsule at the round window area. The spiral ligament was frequently degenerated without any apparent damage to the stria and the sensory cells.

The spiral ligament adjacent to the scala vestibuli was not degenerated except when the coiled arteries were occluded. While no hemorrhage was seen within this part of the spiral ligament, the small amount of blood seen in the adjacent perilymphatic space probably came from vessels in this area. The spiral ligament adjacent to the scala tympani contains numerous collecting venules. Hemorrhage was seen around these vessels as early as one hour after venous obstruction. Hemorrhage within the spiral ligament was severe one or two days after obstruction but about one month later no trace of blood could be identified. Phagocytic activity was evident everywhere within the spiral ligament.

External Sulcus Cells. The first change noted was pyknosis and fragmentation of nuclei accompanied by extreme swelling of cytoplasm (1-24 hours). The cells in the basal turn were most affected. The apex showed no abnormality. The spiral ligament was usually degenerated in the area where the nuclei of the external sulcus cells were absent (Fig. 7B). Blood and pigment granules were seen within the external sulcus cells in a few instances.

Supporting Cells. The nuclei of Deiter's cells were found below their normal position in the region where outer hair cell nuclei were lost except in the apical turn (see Figs. 3C, 9, 10). In the extremely degenerated cochlea obstructed for five months there was only a slight reduction in number of Deiter's cells, pillar cells, Hensen,

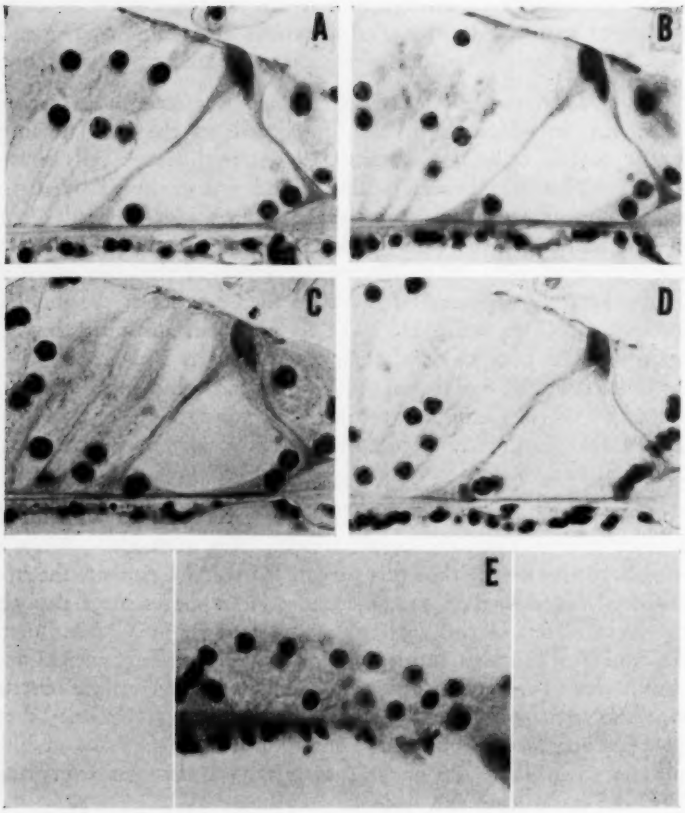

Fig. 3.—Progressive changes in the sensory cells and supporting cells of the organ of Corti after sudden venous obstruction.

A. Normal
B. 1 day
C. 7 days
D. 1 month
E. 5 months.

Claudius, Boetcher and mesothelial cells. The basilar membrane itself appeared to be unaffected (Fig. 7C).

Tectorial Membrane. An occasional abnormality was seen in the severely damaged ear.

Limbus Spiralis. The limbus spiralis showed changes as early as 12 hours. The lesions were sporadic and often located in the area adjacent to the internal sulcus cells. The cells within Huschke's teeth were very rarely affected (see Fig. 7B).

Reissner's Membrane. An occasional specimen showed swelling and reduction of the cells as well as pigment granules. The position of the membrane showed considerable variation within normal limits but partial collapse was suggested in a few cases (see Fig. 6).

Cochlear Duct. Varying amounts of extravasated blood from the strial capillaries was seen in the scala media up to seven days after obstruction (Fig. 8C). Cellular fragments and pigment granules released from the degenerating stria were present throughout the experimental period (six months) (Fig. 8D). The released cellular elements did not appear to aggregate at the basal end of the cochlea or at the cochlear end of the ductus reuniens. Red blood corpuscles were found in the midlength of the ductus reuniens in four specimens at one to seven days. However, this blood was located adjacent to the subepithelial hemorrhage in every instance and in one of the specimens could be followed directly into the lumen of the ductus reuniens.

Free phagocytes were rarely seen in the scala media. The blood and cellular fragments within the cochlear duct appeared to disintegrate. The phagocytic cells in the endolymphatic sac although not always increased in number, frequently contained more yellow, brown or black granules compared with the control side.

Perilymphatic System. A varying degree of extravasated blood was observed in the perilymphatic spaces of the majority of cochleae following venous obstruction. In the first hour it was found adjacent to the collecting veins in the peripheral part of the scala tympani throughout the cochlea. By the sixth day most of the blood was found aggregated in the upper turns (Figs. 8A and B). Throughout the rest of the experimental period the blood remained in these areas and phagocytosis was very active. After five months all traces of blood had disappeared.

The mesothelial cells showed phagocytic activity within two days and later migrated out into the large hemorrhagic mass within the perilymph.

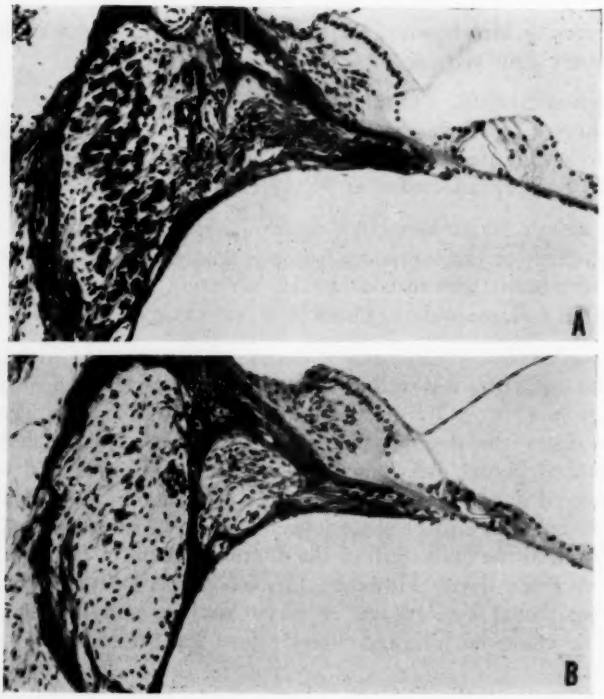

Fig. 4.—Spiral ganglion, nerve fiber and end organ degeneration five months after venous obstruction.
B. Normal control, corresponding level (2nd turn) is seen in A.

COMMENT

Obstruction of the inferior cochlear vein without interfering with its collaterals produces minimal changes as reported earlier by one of us. In that experiment no change in the electrical responses or sensory cell damage was demonstrated but rupture of vessels in the stria vascularis with bleeding into the cochlear duct was seen in a few animals. As recently reported the marked change in blood flow following the more complete obstruction was particularly noticed in the strial capillaries. This is due to the fact that the flow in these vessels is normally slower and at lower pressure than in the other vessels of the spiral ligament. Dilation of the strial capillaries was marked. No spontaneous vasomotor activity such as spasm of the arterioles could be seen.

Definite histopathologic changes in the cochlea were produced in this experiment. These varied greatly in degree, extent and structure involved. Graphic reconstructions of some of these lesions are seen in Figures 9 and 10. Even in these animals with more extensive venous obstruction 18 per cent showed no sensory cell damage. The remainder however showed various degrees of histologic damage to sensory cells.

Outer hair cells degenerated earlier than inner hair cells. This is in agreement with the finding from other types of experiments and observations in hereditary deafness. Histochemical tests and reactions to vital staining also suggest differences in the physiology between the outer and inner hair cells.

Some discrepancies were found between the extent, degree and time of onset of changes in the spiral ganglion cells and in the outer hair cells (see Figs. 9 and 10). Other pathological conditions of the cochlea have also shown these discrepancies. In our experiment the severe hair cell damage without corresponding ganglion cell loss may be due in part to a collateral blood supply to the spiral ganglion and its greater inherent resistance to anoxia.

Lurie[5] on the basis of his findings in the waltzing guinea pig found no correlation between lesions of the organ of Corti and of the stria vascularis. In this experiment a correlation between damage to the stria and sensory cells was particularly good in the basal turn where changes were most commonly seen. In other turns the correlation was less evident and only in the case of extensive lesions was the association evident.

For example, absence of the stria in the apical 8 mm of the cochlea was seen in a control animal with normal hair cells.

Hypertrophy of the stria epithelium containing dilated capillaries and clear globules on the surface of the cells are seen after venous obstruction but their significance is not clear.

The degenerative change in the spiral ligament adjacent to the cells of Claudius and external sulcus cells was well circumscribed and was independent of changes in the adjacent stria. In the control cochleas with strial atrophy the spiral ligament appeared normal.

The external sulcus cells were also definitely affected. The function of these cells is obscure. Both an absorptive and secretory function have been suggested and phagocytic activity has been described. In this experiment the cellular fragments released into the scala media were not particularly numerous around the external sulcus cells. However, a small amount of phagocytosis was observed here.

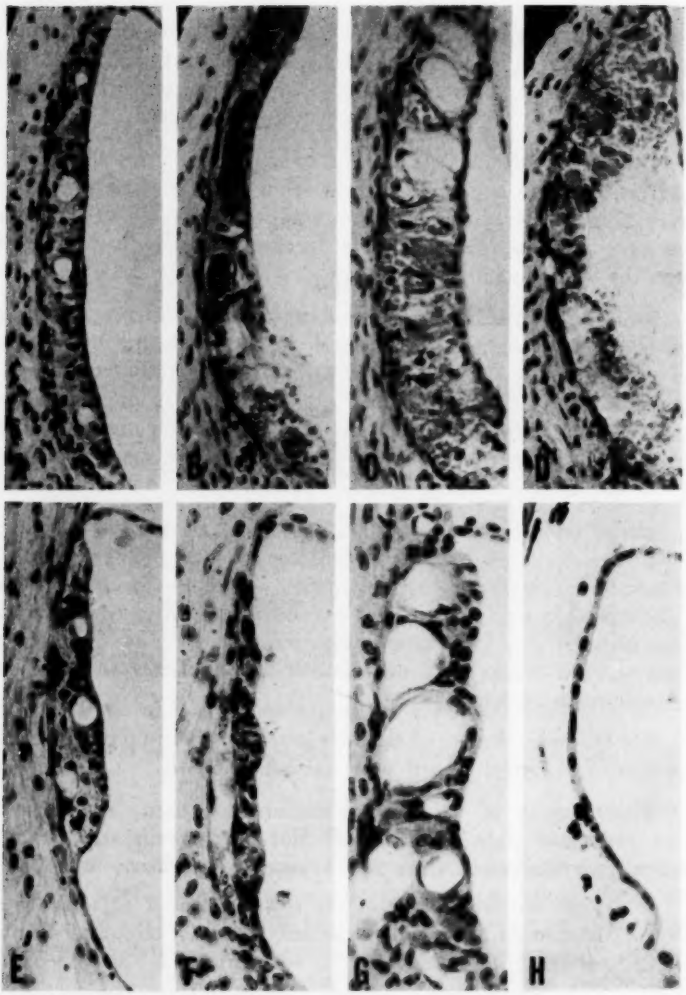

Fig. 5.—Various degrees of acute (within 24 hours) (B, C, D) and chronic (up to 6 months) (E, F, G, H) changes in the stria vascularis. A is normal. See text for details.

Fig. 6.—Mid modiolar section through cochlea five months after sudden venous obstruction showing extensive changes. See graphic reconstruction bottom of Figure X. Note the changes in the spiral ligament, i.e. reduced cellular density and partial collapse of Reissner's membrane.

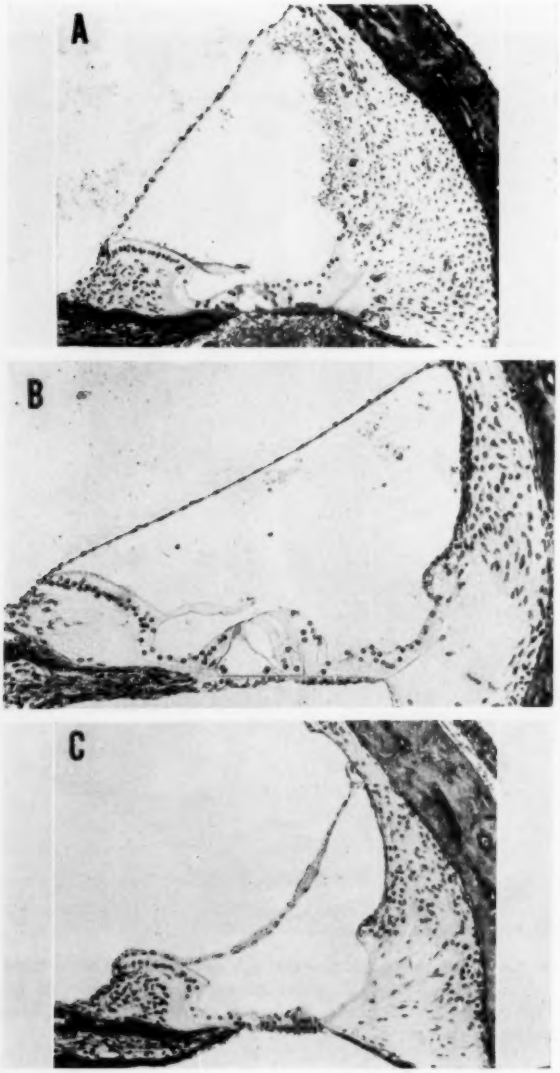

Fig. 7.—Acute and chronic changes in scala media after sudden venous obstruction.

A. One day. Note fragmentation and hemorrhage of stria vascularis.

B. Five months. Note reduced cell density in spiral ligament and spiral limbus.

C. Five months. Note severe degeneration of end organ and stria.

These cells were among the first to be affected by venous obstruction. These findings do not resolve the question of the function of the external sulcus cells.

Migration of the nuclei of Deiter's cells toward the basilar membrane was a consistent early finding. These changes corresponded with outer hair cell degeneration except at the apex. However, no conclusions as to the functional relationships between Deiter's cells and the outer hair cells can be made on the basis of these findings.

Spotty degeneration of the limbus spiralis was also produced by this lesion probably related to the particular arrangement of vascular loops in this area.

Because of the variations in the position of Reissner's membrane in the control ears changes in the operated ear were difficult to assess. However, suggestive evidence of collapse was seen in a few cases. In addition swelling and reduction in cells of Reissner's membrane were occasionally observed. Significant changes in Reissner's membrane were more readily apparent in this experiment because both the normal and operated temporal bones and the intervening brain were preserved as one block. About 10 per cent of the control cochleas in this series showed abnormalities in the position of Reissner's membrane.

The absence of hydrops of the cochlear duct was particularly significant since it provides strong evidence that the pathogenesis of the hydrops seen in Ménière's disease is probably not related to acute venous obstruction.

In contrast to the findings of Guild[6] this experiment revealed no definite evidence for endolymph movement. There was no accumulation of the blood or cellular fragments at the basal end of the cochlear duct. Blood was found in the ductus reuniens in a few cases but in these instances it appeared to come from subepithelial hemorrhage immediately adjacent to the ductus. However, in the older preparations, the endolymphatic sac on the operated side showed more pigment containing phagocytes than the sac on the normal side.

The disappearance of cellular debris in the scala media has been explained by molecular disintegration[7] and by phagocytosis of the endothelial cell in the strial capillaries[8] and by phagocytosis of the external sulcus cell.[9] Our experiments revealed evidence for all these activities. In addition areas of phagocytic activity in the endosteum and spiral ligament were observed. Free phagocytes were also seen in the scala media when there was a large quantity of cellular debris.

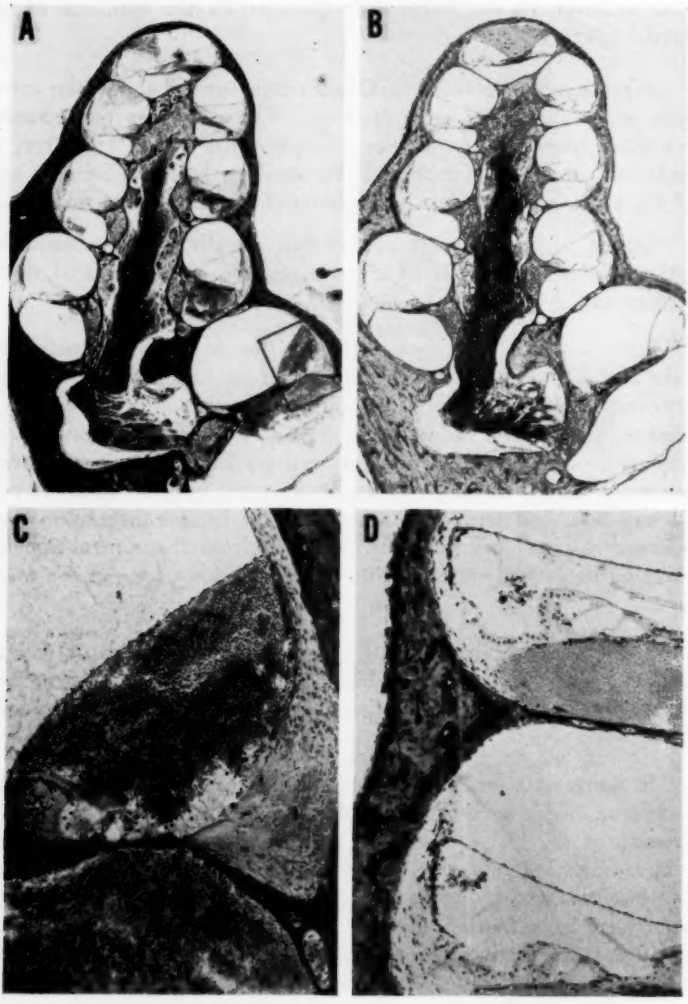

Fig. 8.—Distribution of blood and cellular elements in the endolymph and perilymph.

A. 24 hours.
B. One month.
C. Severe hemorrhage area bracketed in A.
D. Pigment and cellular debris released from stria one month.

Practically all the hemorrhage in the perilymphatic space throughout the cochlea came from collecting venules and veins in the scala tympani. Blood accumulated in the upper turn of the cochlea but did not appear to move towards the vestibule. Cellular fragments in the scala media remain adjacent to their source in the stria indicating little or no endolymph movement. However, the migration of the blood cells in the scala tympani towards the helicotrema is suggestive of movement of the perilymph. This might be related to the travelling waves in the basilar membrane produced by acoustic stimulation.

Several animals were decapitated for the purpose of determining whether the amount and distribution of the blood and the site of hemorrhage was different from the perfused specimens after sudden venous obstruction. In the perfused cochlea of one to two days, the amount of free blood may have been slightly larger, but the distribution and site of bleeding were the same as in the decapitated animals.

The presence of extravasated blood cells in the labyrinthine fluids has been known to be compatible with the normal appearance of sensory elements. In these experiments no correlation could be found between the amount and extent of the blood and the sensory cell lesions. Indeed, some cochleas showed no hemorrhage whatsover. Polymorphonucleated white cells were no longer seen among the red blood cells after two weeks, but a small number of lymphocytes and larger phagocytes remained as long as red blood corpuscles were present. This is a well known pathological change that helps to distinguish fresh from old hemorrhage and was described in cochlear hemorrhage by Schuknecht.[10]

The findings in this experiment indicate that at least a major part of the venous drainage of the cochlea is carried by the inferior cochlear vein and that when occluded at the level at which some of the collaterals are also obstructed profound changes in the inner ear can be produced. This suggests that even in man despite the well developed tributaries toward the internal meatus and endolymphatic sac a sudden obstruction of the inferior cochlear vein might produce severe auditory and vestibular disturbances. A slowly developing venous obstruction might however be asymptomatic as it could be compensated for by the collateral circulation. The postmortem changes which have been unavoidable in human temporal bones would make it difficult to detect this type of vascular lesion and its effect upon the sensory elements.

Histologic studies of the changes in the vestibular apparatus in these animals will be presented in a separate report.

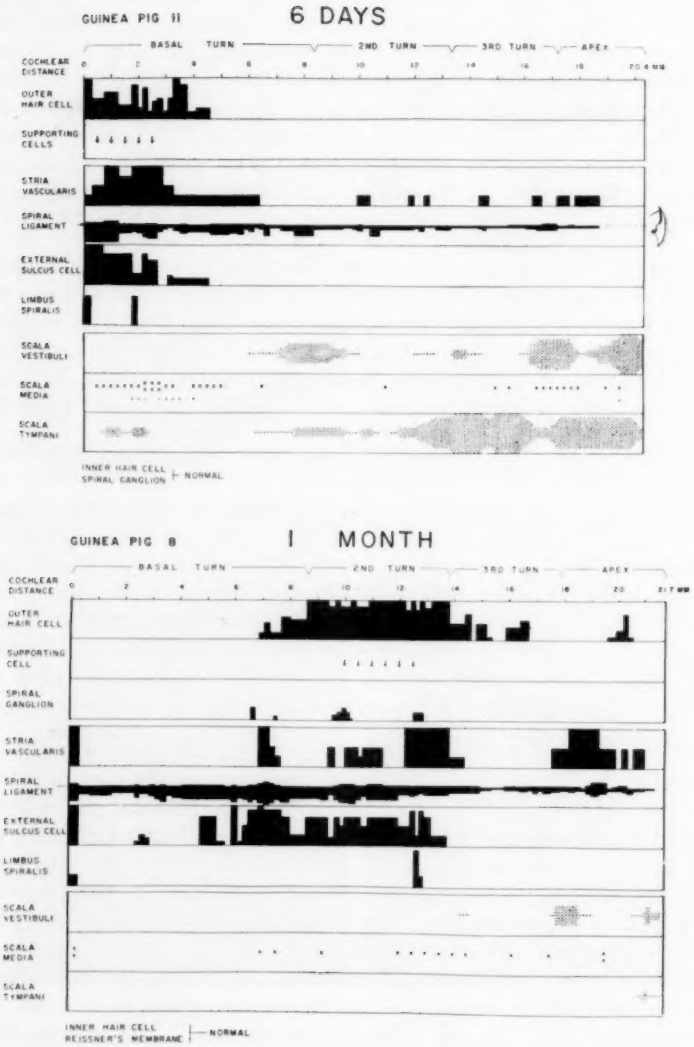

Fig. 9.—Plot showing varying degrees of change in different structures of the cochlea.

Fig. 10.—Plot showing more extensive damage.

SUMMARY

The histological changes which followed surgical obstruction of the inferior cochlear vein and some of its collaterals in the guinea pig were profound.

Degeneration of the sensory epithelium was seen in 82 per cent of the animals. The external hair cells degenerated earlier than the internal hair cells following acute venous obstruction.

Various stages of degeneration of the stria vascularis and of the area of the spiral ligament adjacent to the external sulcus also occurred. The earliest changes appeared in the stria and spiral ligament. Parallel degrees of change in the stria vascularis and the sensory cells were most evident in the basal coil where lesions were frequent.

In the early days after venous obstruction varying degrees of hemorrhage into the labyrinthine spaces occurred. This appeared to come from the strial capillaries and particularly from the collecting venules. Reissner's membrane, tectorial membrane, basilar membrane and other structures in the cochlea showed minimal or no change after venous obstruction.

950 E. 59TH ST.

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XXVIII

CARBONIC ANHYDRASE AND INTERNAL EAR

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Carbonic anhydrase is a very widely distributed enzyme in the human body. It is found in high concentration in the blood's red cells, renal cortex and gastric mucous membrane. Using the semi-quantitative method described by Robinson,[2] Alcocer and Corvera found a high concentration of carbonic anhydrase in the guinea pig's cochlea. This work shall be presented at a future date.

The carbonic anhydrase catalizes in the tissues the following reactions: $H_2O + CO_2 = H_2CO_3$, which having a pKa of 6, ionizes into hydrogen and bicarbonate ions. This reaction is inhibited by numerous agents, among which sulfonamide[3] and acetazolamide[4] are to be found.

The inhibition of the carbonic anhydrase in the renal parenchyma decreases the available hydrogen ions, which not being excreted will result in a compensating elimination of sodium. Urine is alkalinized and water is lost. Therefore, it is used as a diuretic.

In the eye (an organ rich in carbonic anhydrase), it acts, allowing the reaction between the hydroxyl ions produced by the cytochromic epithelium and the carbon dioxide present, so as to produce $H+$ and $HCO_3—$. This radical passes into the aqueous carrying cathions, mainly of sodium. The acetazolamide which inhibits the reaction producing HCO_3 will permit the decrease of electrolytes of high osmotic pressure (sodium and others) in the aqueous, and therefore the decrease of the intra-ocular pressure.

In view of the relationship reported by some authors[6] between the glaucoma and the labyrinthine hydrops, as well as the improvement experienced with a low sodium diet, we felt it would be interesting to study the relationship between carbonic anhydrase and acetozolamide in patients having Ménière's disease, from the clinical as well as the experimental point of view. This work represents the clinical side and constitutes a preliminary report on the results obtained by the treatment of Ménière's disease with acetazolamide (Diamox Lederle). The first part consists of a brief summary of the physiologic fundamentals on which it is based and is followed by the results obtained in six patients.

COMPOSITION OF THE LABYRINTHINE LIQUIDS

The endolymph and the perilymph are constituted by a suspension of proteic macramolecules of a high molecular weight, ordered in heaps and chains[7] and of a concentration which is approximately the double in the perilymph to that of the endolymph and being approximately equal in the endolymph and in the spinal fiuid. The osmotic pressure of the endolymph is higher than that of the perilymph,[9] which is explained by the greater concentration of electrolytes in the former.[8]

Kaeida,[10] studying the electrolytic composition of the labyrinthine liquids in the shark, in relation to sodium, potassium and chlorides, found values which were very similar in the endolymph, perilymph and spinal fluid, but Smith, Lowry and Wu[8] in a very precise study performed in guinea pigs, found that the endolymph contains ten times less sodium than the perilymph, thirty times more potassium and a 90 per cent of the concentration of the perilymphatic chlorides, while the perilymph and the spinal fluid are similar in their electrolytic composition.

Graf and Poreti[11] measure the speed of penetration of radioactive sodium of the spinal fluid into the labyrinthine liquid, finding that after six hours the perilymph has a concentration of 82 per cent in respect to the spinal fluid, but that the endolymph has gone up to 9 per cent only. These values are in accordance with the low concentration of endolymphatic sodium reported by Smith et al.

Vilstrup and Jensen[12] report the presence of hialuronic acid (or another substance of similiar behavior) in the endolymph of *Acanthias Vulgaris.*

PLACE OF ORIGIN AND REABSORPTION OF THE ENDOLYMPH

Mygind[13] points out that the epithelium of the endolymphatic system is the place for the production of the endolymph through active secretion. Scuderi[14] thinks that it has a double origin, plasmotic ultrafiltration and active secretion through the stria vascularis. This last formation is considered by Saxen[15] and Guild[17] and confirmed by Ruedi, as the origin of endolymph. They used fluorescine, radioactive phosphates and radioactive sodium chloride respectively.

The place of absorption is far more discussed. The studies carried out by Arnvig,[18] Engström[16] and Guild[17] with India ink, give a very important role to the pars intermedia of the endolymphatic sac. The importance of this origin is doubted by Lindsay et al.,[19] who do not find any histological alteration in the ears of animals whose endolymphatic and periotic ducts were obliterated. Lempert

et al.[2] do not find any evidence as to the function of this organ and consider it only as vestigial.

Scuderi,[14] Saxen[15] and Graf et al.[11] consider the sulcus spiralis and limbus laminae spiralis as important places of absorption and the pars intermedia as secondary.

Let us consider that this data, specially those conditions that reveal the peculiar electrolytic composition of the labyrinthine liquid, can permit us legitimately to work out a thesis that considers the labyrinthine hydrops as an immediate result of an increase of the osmotic pressure of the endolymph, regardless of the etiological cause of the disease.

REPORT OF CASES

CASE 1. The patient, a woman, 45 years old, 18 years before the date of the study presented intense vertigo in the eighth month of her first pregnancy which disappeared two months after a normal childbirth, but which resulted in an accentuated deafness in the left ear. She has had four more pregnancies without the symptoms repeating themselves, until two weeks ago, when the deafness became worse, accompanied by generalized tinnitus of medium intensity and rotatory vertigo of slight intensity that presents itself several times a day and which lasts from two to ten minutes. Audiometry reveals a severe left ear deafness of the perceptive type. Therapeutic treatment was established with a dosage of 250 mg daily of acetazolamide. On the third day the dizziness disappeared and on the eighth the tinnitus was hardly noticed. Audiometry shows no change whatsoever.

CASE II. The patient, a male, 46 years old, presented two months ago, right deafness and tinnitus, progressively intensified, rotating vertigo, which lasted from two to twelve hours. Audiometry revealed bilateral perceptive hypoacusia, more intense in the right ear. After eight days of treatment with acetazolamide vertigo disappeared and after two months of constant treatment audiometery showed an improvement in hearing, with a gain of 25 db in 8000 cycles in the right ear.

CASE III. The patient, a male, 47 years old. Since about a month ago, he had presented dizziness occurring several times a day and lasting from two to ten minutes approximately, accompanied by acute tinnitus and deafness. Audiometry revealed bilateral perceptive hypoacusia which was more accentuated on the right side. After seven days of taking acetazolamide, the dizziness disappeared and 21 days later the tinnitus and the deafness remained the same.

CASE IV. The patient, a woman, 32 years old, has suffered an allergic rhinitis in the summer months, for six years, as well as urticaria on several occasions. Starting ten days previously, she had daily episodes of objective rotatory vertigo, accompanied by tinnitus of medium intensity, right deafness and nausea. The dizziness stopped in five minutes more or less and the tinnitus and the hypoacusia lasted for about an hour. After three days of taking acetazolamide the symptomatology stopped completely. The audiometry which only showed a fall of 15 db in 4000 cycles for the right ear exclusively, remained the same after a week.

CASE V. The patient, a male, 24 years old, presented vertigo lasting two minutes and occurring around six times a day. There was deafness and tinnitus all the time in the right ear, that lasted for ten days. Audiometry revealed right deafness with a descending curve that went from 45 db to 60 db. Three days after the treatment with acetazolamide was started, the dizziness disappeared; ten days later hearing and deafness improved. (Patient treated and controlled by Dr. Mariano Hernández.)

CASE VI. A male patient, 27 years old, worked in noisy surroundings. He complained of tinnitus and bilateral progressive hypoacusia for a period of six months. At the beginning of the disease, vertigo presented itself on three occasions and lasted for ten minutes, but has not since occurred. Audiometry revealed a bilateral and abrupt fall at 4000 cycles (60 db for the left ear and 85 db for the right ear). At 8000 cycles it was 70 for the left ear and the threshold could not be found in the right ear. Acetazolamide, proteins, lipotropics and vitamin B-12 were prescribed. Two months later there was improvement of the tinnitus and subjective improvement of hearing but the audiometry remains the same.

SUMMARY

Acetazolamide was administrated in doses of 250 mg daily, for a length of 21 to 63 days, to six patients of Ménière's disease, whose ages vary from 24 to 47 years. In all the cases, vestibular caloric tests were carried out, as well as a complete neurological examination.

The acetazolamide caused the vertigo to disappear in all cases in periods of three to eight days. Improvement in hearing was present in four of the six cases, in four days to two months. Only in one case did the hypoacusia improve with a continuous treatment for two months.

Even though this work cannot present definite conclusions because of the small number of cases, it can indicate to what extent it

can be of interest to study the use of acetazolamide in the treatment of labyrinthine hypertension.

Rio Tigris 120

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XXIX

MULTIPLE PARAGANGLIOMAS IN THE HEAD AND NECK

CASE REPORT

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Paragangliomas occurring in the head and neck are rare tumors. These neurogenic tumors are classified as nonchromaffin neoplasms. They originate from chemoreceptor tissues along the glossopharyngeal nerve, vagus nerve and adventitia of the carotid arteries and jugular veins. Physiologically, they are associated with chemoreceptor activity. Biologically, the vast majority are benign, although there is indisputable evidence of regional and generalized metastasis in a small group of cases. Microscopically, epithelioid cells are scattered in a well vascularized fibrous structure. Mitosis is rarely seen and a benign microscopic picture does not necessarily guarantee a benign clinical course. Approximately 350 carotid body tumors and 102 glomus jugulare tumors have been reported in the literature. Multiple and bilateral paragangliomas in the head and neck are exceedingly rare.

These tumors are asymptomatic in their early stages of development. As they increase in size they may cause pain, pressure, syncope or affect a special organ. This is particularly true in glomus jugulare tumors where vertigo, deafness, cranial nerve involvement and discharge from the ear may characterize the advanced cases.

The treatment is surgical removal, when this is possible without undue risk to the patient's life. Small carotid body tumors are resected without injury to the carotid arteries. Large carotid body tumors may require carotid artery repair or free vessel anastomosis. Small glomus jugulare tumors are resected by radical mastoid approach. Large glomus jugulare tumors require opening the upper neck and occasionally the cranial cavity. These latter cases are associated with cranial nerve paralysis, severe hemorrhage and high operative mortality.

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REPORT OF A CASE

M. B., white female aged 26, was first seen in March 1954 with an asymptomatic lump in the left neck. It had been present for approximately three weeks, was gradually increasing in size but was not associated with pain, pressure or syncope. Examination of the head and neck revealed moderate, diffuse, bilateral, cervical lymphadenopathy with the presence of a firm node in the region of the carotid bifurcation on the left side. It was intimately associated with carotid artery pulsations and not compressible. There were paralysis, atrophy and fibrillations on the right side (contralateral) of the tongue, with inability to protrude this side of the tongue. The left side of the tongue was normal. There was a complete nerve type deafness in the right ear which the patient stated had been present as long as she could remember. There was a definite history of severe intermittent dizziness several years previously, which resolved spontaneously. There were no spontaneous signs of labyrinthine irritation at this time. The labyrinth was normally active to ice water tests. Both ears appeared normal. X-rays of the mastoid area were normal. Complete preoperative medical survey was unrevealing.

In October, 1954, a carotid body tumor was removed from the bifurcation of the internal and external carotid arteries at the level of the carotid bulb, on the left side. This tumor was bloody, tenacious, and adherent to the adventitia of the carotid vessels, but came off without any unusual incident by tedious dissection. The tumor measured 3 x 5 cm. The carotid arteries were not injured in any way. The vagus and hypoglossal nerves and sympathetic chain remained intact. The patient's postoperative course was uneventful.

In June, 1955, the patient complained of a sensation of fullness in the right ear and examination revealed a reddish prominence entering the tympanic cavity from the region of the jugular bulb. The tympanic membrane was intact. This finding had not been noted on the previous examination. There was a total perceptive loss of hearing in the right ear. Ice water tests revealed the labyrinth to be normally active. Repeat x-rays of the mastoids and base of the skull with particular attention to the jugular bulb, carotid artery and cochlea were unrevealing for any bone destruction. In July, a 1 x 2 cm glomus jugulare tumor was removed from the right ear through an endaural approach. It arose from the dome of the jugular bulb in the region of the floor of the tympanic cavity, extended forward toward the eustachian tube and medially into the inferior part of the cochlea with destruction of the inferior aspect of the promontory of the cochlea at this site. There was also destruction of the bone behind the descending portion of the facial nerve and extending

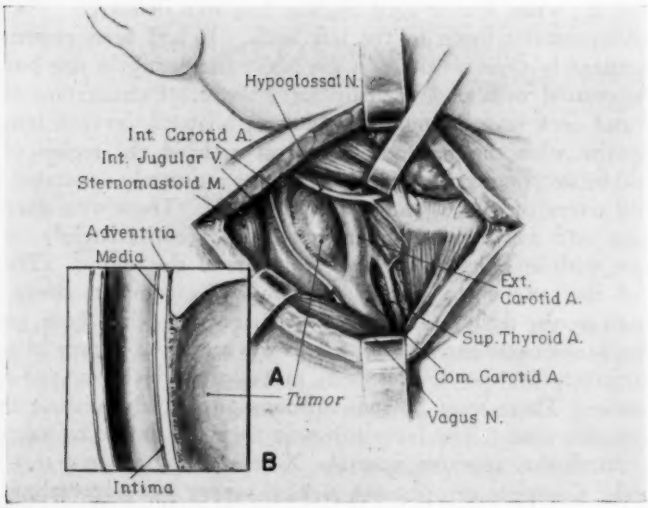

Fig. 1.—A. Small carotid body tumor. B. Relationship of carotid body tumor to media.

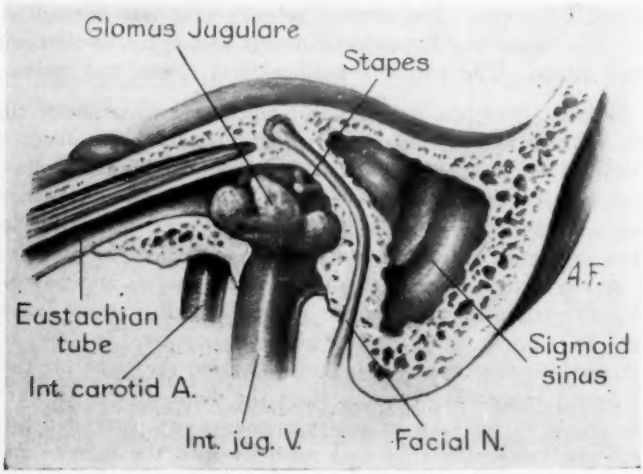

Fig. 2.—Glomus jugulare tumor and its relation to adjacent tissues.

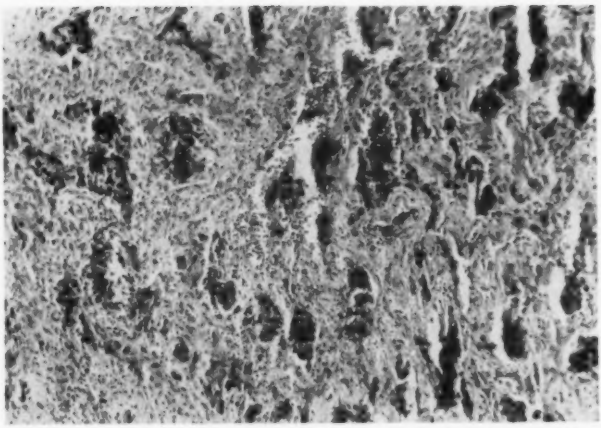

Fig. 3.—Carotid body tumor. The tumor consists of rather large, pale, rounded or somewhat elongated epithelial cells with relatively small nuclei, none of which were found to be in mitosis at the time of examination. These groups of cells are separated from each other by delicate fibrous strands in which there are numerous vascular spaces.

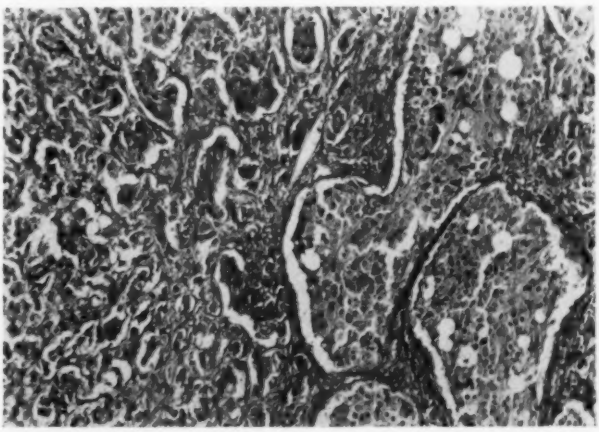

Fig. 4.—Glomus jugulare tumor. The tumor consists of dense, somewhat hyalinized fibrous tissue in which there are groups of elongated and polyhedral tumor cells with scanty acidophilic cytoplasm. Some of the islands of tumor cells appear compressed and these appear as small hyperchromatic nuclei. No malignant change is evident.

toward the posterior fossa. The tumor at its widest portion was approximately 2 cm in diameter. Nothing unusual occurred during this operation. The facial nerve was not injured. There was no excessive bleeding. Postoperatively the patient had severe vertigo for a period of about ten days. This gradually subsided. On the seventeenth postoperative day the patient developed a weakness of the lateral rectus muscle on the right side. She had fallen, upon getting out of bed, striking her head, and it was thought that this paresis might be associated with the accident. This cleared slowly over four months. X-rays of the skull did not reveal any fracture. The patient is asymptomatic.

SUMMARY AND CONCLUSIONS

A case of multiple paragangliomas, one existing in the left carotid bulb area (carotid body tumor) and the other existing in the right tympanic cavity (glomus jugulare tumor) is reported.

Both conditions were removed surgically without any unusual event. The carotid body tumor was resected without injury to the carotid arteries or vagus, spinal accessory or sympathetic nerves. The glomus jugulare tumor was removed without injury to the facial nerve and without severe hemorrhage.

The tumors have behaved clinically as benign tumors.

This patient has recently had complete investigation which failed to reveal any abnormalities.

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XXX

THE FINE STRUCTURE OF TASTE BUDS AND TASTE FIBRES

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In otorhinolaryngology we often find, in connection with injuries and diseases in the mouth, the pharynx and the ears, changes in peripheral taste receptors and taste fibres.

In modern otosurgical work injuries are often caused, intentionally or accidentally, to the neural pathways for taste. In such cases it is generally the chorda tympani, which is severed. The course of this nerve, running unprotected within the middle ear, makes it especially vulnerable.

Our facilities to test and evaluate changes caused in this way are still very limited and this has prompted us to take up the study of the sense of taste. As part of this work the present publication forms a light- and electron microscopic investigation of the structure of taste buds and peripheral taste fibres.

The basic principles in the structure of taste buds have earlier been described. It has been shown that in mammals the sense of taste has its peripheral receptors arranged in special sensory organs, the so-called taste buds or calyculi gustatorii. These buds are, in the more highly developed animals generally found in the mouth, mostly on the tongue, but they may also appear to a lesser extent in the pharynx and the larynx. Similar formations were earlier described in fish. In human beings the taste buds seem to be more plentiful in children than in adults. A noticeable reduction in the number of taste buds is observed with increasing age. It is of interest, in this connection, that the reduction is mainly to be found in the anterior part of the tongue. In children the taste receptors are thus more frequent on the anterior part, whereas adults have a comparatively large number on the posterior parts of the tongue.

From the Ear, Nose and Throat Clinic of the University of Göteborg.

Fig. 1.—Foliate papillae (FP) from the tongue of a rabbit. Staining: Hematoxylineosin. TB = taste bud; S = sinusoid; G = gland. Light microscopy.

The taste buds are, in the main, localized in certain definite regions of the tongue and the foliate and circumvallate papillae contain the largest numbers. Taste buds also appear outside the papillae, scattered in the mucous membrane of the tongue. In children and young animals they are also found on the papillae fungiformes.

Among the animals mostly studied is the rabbit, in which the taste buds appear in large numbers in the foliate region on the posterior part of the tongue. In this region the foliate papillae form two distinct groups of ridges, divided by taste furrows. Along the sides of these furrows a large number of taste buds are gathered.

With regard to the general structure of the taste buds, there is unanimous agreement that they are well distinguishable from the surrounding epithelium and the underlying connective tissue. It is possible to recognize a base, curved sides and a top in each taste bud. The top contains the taste pore which forms an excavation on the surface of the taste furrow. In the taste pore delicate processes, the taste hairs, protrude. The taste buds vary in shape in different animals. They are sometimes almost round, sometimes spindleshaped.

They generally lie separate from each other as single buds, but compound buds with several taste pores have been described by Heidenhain and others.

With regard to the different types of cells found in the taste buds there are many diverse opinions.

For instance, Olmsted[28] described in Ameiurus only one type of gustatory cells.

Lovén,[24] Schwalbe[37] and others distinguished between peripheral supporting cells and central taste cells.

Kolmer[7] observed different types of sustentacular and gustatory cells and believed that these were constantly changing from one type to another.

Ranvier[32] believed that he had discovered that supporting cells also occurred centrally between the taste cells, as previously had been described by Merkel.

Hermann[15,16] distinguished between sensory cells and two forms of supporting cells, pier cells (Pfeilerzellen) and rod cells (Stabzellen). He also described basal supporting cells in the lower part of the taste buds.

Von Lenhossék,[21] who found four separate types of supporting cells, could not, however, verify any basal cellular elements.

Grâberg[12,13] "rediscovered" supporting basal cells and distinguished further between central and peripheral supporting cells. In addition he stressed the importance of the epidermal cells immediately next to the taste buds, which he called extrabulbar cells.

It is evident that much confusion exists regarding the structure of the taste buds.

At first there was also pronounced uncertainty over the innervation of the taste buds. Basic research, however, has shown that the taste fibres, near the base of the taste buds, shed their myelin sheath and thereafter finish as intercellular nerve endings between the epithelial cells of the taste bud. These "intragemmal" fibres often reach the upper part of the buds, where they sometimes form club-like endings.

According to authors who distinguish between different types of sensory or sustentacular cellular elements, the intragemmal fibres innervate all of them. According to our present opinion the intragemmal fibres form a close contact with the cells, without entering them.

Fig. 2.—Taste bud in the skin of a salamander. Light microscopy.

A rich nerve supply, however, is also found within the region around the taste buds, which favors the opinion that the epithelial region nearest to the taste bud can be of importance. These fibres are generally called intergemmal fibres.

In the foliate region of the rabbit it is possible to distinguish ridges and between these ridges there are furrows into which the taste buds and the gustatory glands open. The epithelium of the taste furrows is, in its uppermost layer, cornified. The cells nearest to the taste bud seem to form a region of very pronounced enzymatic activity. The greatest enzymatic activity is found in a region of 2-3 μ around each taste pore.[3] At the base of the furrow there lies still another region, which also shows a high enzymatic activity. The cellular nuclei in this place are rounded and the cells have a distinct cellular membrane. This region shows a rather pronounced basophilic staining reaction and contains large amounts of phosphatase.

It is probably of significance that the taste buds occupy the whole thickness of the epithelium and that they are free from surrounding epithelium at the top, as well as at the base. At the base the taste buds form direct contact with the underlying connective tissue. This tissue contains, among other structures, the subepithelial nerve plexus, which supplies the taste buds with nerve fibres.

Baradi and Bourne[3] have pointed out that the region below the taste buds contains sinusoids. These cavities are composed of blood-filled sinuses bordered by endothelial cells. They communicate with larger sinusoids, forming a rich network below the taste ridges. Baradi and Bourne have also drawn attention to the small cavities in the region around the taste buds. The importance of these sinusoids is still unrecognized, but it is believed that they contain blood which continuously clears the taste region from taste substances.

A problem of great significance regarding taste has been discussed by Baradi and Bourne in a recent publication. Using different histochemical methods these authors believe they have shown that the taste epithelium and the surrounding tissues have a pronounced enzymatic activity. Their investigations have mainly been carried out on the foliate region of the rabbit, where they report the occurrence of hexosediphosphatase, adenosinetriphosphatase, acid phosphatase, esterase and lipase. They assume that the different parts of the taste epithelium and that taste substances in a regular way influence the enzymatic activity. Baradi and Bourne have also formed a theory, according to which the enzymatic activity could influence the formation of nerve impulses in the taste fibres, and in that way also the perception of taste. According to their point of view the taste buds, together with the surrounding tissues, would form a complicated organ of taste. This theory assumes that there are considerably more possibilities of combination of taste qualities, than is generally accepted in neurophysiological literature, where only four or five taste qualities are described (sweet, sour, salt, bitter and the taste of water).

MATERIALS AND METHODS

This paper consists of a light- and electron microscopic investigation into the structure of taste buds and peripheral taste fibres.

The light microscopic study, carried out with ordinary preparation and staining methods, has been undertaken on a large number of lower and more highly developed animals as well as on human beings. For the staining of the nerves methylene blue and Golgi and Palmgren staining techniques have been used.

For the electron microscopic investigation we have mostly used foliate papillae from the rabbit. In the foliate papillae of rabbits an unusually large number of taste buds is found in a well defined and circumscribed area. These taste buds can easily be recognized at the preparation of the material.

Immediately after the decapitation of the animals the foliate region has been excised, divided into suitable parts and fixed in a 1

Fig. 3.—Taste pore (TP) with filiform processes. Electron microscopy: 15000x.

per cent veronal-buffered osmic acid solution (according to Palade and modified by Sjöstrand). After acrylate embedding the specimens have been sectioned with a Sjöstrand microtome for ultra-thin sectioning. The electron microscopic examination has been carried out with an RCA microscope (type EMU 2 c).

STRUCTURE OF THE TASTE BUDS

In the rabbit the foliate papillae contain a large number of taste buds appearing either as single or compound buds. The latter may contain up to five or six taste pores. The taste buds are clustered

Fig. 4.—Innervation of taste buds in the fish Gobius. Preparation by Retzius. Staining: Golgi. Photography by the authors. Light microscopy.

together along the furrows in the foliate region and they open into the furrows by their taste pores.

The different taste buds are generally rounded with a base, curved sides and a top where the taste pore opens into the furrows between the taste ridges. The nerve fibres enter or leave the taste buds at the base, forming a connection between the taste buds and peripherally or centrally located ganglion cells.

The taste buds consist of a number of elongated epithelial cells intermingled by nerve endings. The epithelial cells are generally long, reaching from the base to the taste pore. The cells show a rich variety in structure and there it is possible to observe very slender, in cytoplasm poor cells, in addition to cells with abundant, richly granulated cytoplasm. There is, however, no distinct way of differentiating between these cell types and it is very probable that they may gradually change from one type of cell into another. In many of the largest cells a considerable number of dissolved granules are found, which probably are secretory products. In the basal part of the cells around the nucleus a membranous structure, to all appearance a Golgi apparatus, is sometimes observed. The uppermost parts of the cells generally have a number of filamentous protrusions into

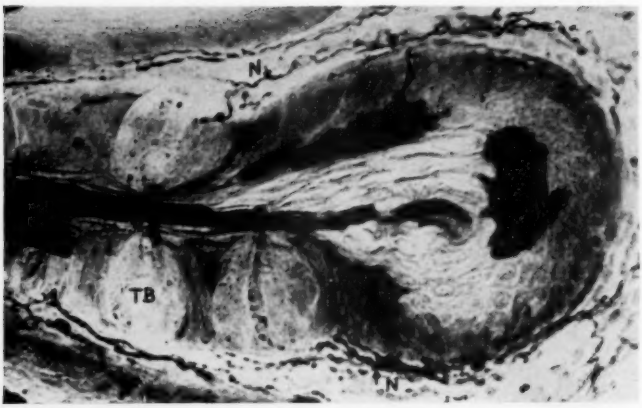

Fig. 5.—Innervation of taste buds from the foliate region of a rabbit. Staining according to Palmgren. TB = taste bud; N = nerve fibres. Light microscopy.

the taste pore. These protrusions, sometimes more than three, four or five on each cell, have a length of 3-5 μ and a diameter of about 0.2 μ. We have never found only one single taste hair on the taste cells as previously described. On the contrary they seem to be rather numerous and in our preparations they have always the shape of thin-walled fingerlike processes with an outer rounded tip. These fingerlike processes seem to have a very thin wall and a very finely granulated, slightly opaque, central protoplasm without any special granulations. They are here called taste villi.

In the osmic acid fixed specimen in the region immediately below these taste villi, the taste cells have a protoplasm containing a varying number of highly opaque granules of a diameter varying between 0.1 μ and 0.3 μ. These granulations do not appear in every cell, but are quite frequent. They are only found in the uppermost part of the taste cells. It is interesting to note that often, in the taste pore between the different taste villi, a substance of the same high opacity is found, possibly a sign of some kind of secretion or resorption.

The cytoplasm is, in some of the taste cells, abundant while, on the other hand, some cells have a very scanty cytoplasm, but otherwise the different cells show in general the same type of structure. Some of the cells, mostly those with an abundant cytoplasm, contain a large number of dissolved granules or vacuoles found in the supranuclear as

well as in the infranuclear region. The cytoplasm of the taste cells also contain a large number of rounded or oblong mitochondria and very small granules or rods.

The nuclei of the taste cells are generally slightly oval with an irregular nuclear membrane and contain at least one nucleolus. In the region around, and especially below the nucleus between the mitochondria and granules we have found a membranous structure, presumably a Golgi apparatus.

Some of the taste cells contain a very large number of dissolved granules or vacuoles giving them a highly irregular appearance in the micrographs.

Although pronounced differences exist between the different taste cells we have not yet been able to distinguish different typical cell components of supporting and sensory nature.

STRUCTURE OF THE TASTE FIBRES

The innervation of the taste buds is, according to literature, much discussed but it is generally assumed that the anterior two-thirds of the tongue is innervated by the lingual nerve, a mixed nerve carrying different forms of impulses such as touch, temperature and pain as well as taste. The taste fibres in fact form the chorda tympani, which joins the facial nerve centrally after having crossed the open space in the middle ear. The posterior part of the tongue and the pharynx are innervated by the IX and X cranial nerves.

There has been much discussion concerning the course of the nerve fibres transmitting sensation of taste from the anterior two-thirds of the tongue. There is now almost unanimous agreement that the chorda tympani conducts all the taste fibres from this region of the tongue. However, from the geniculate ganglion of the facial nerve to the central nucleus several different pathways have been proposed (Cushing,[6] Schwartz and Weddell[39] and others).

Schiff[36] suggested that the taste fibres were transmitted in the great superficial petrosal nerve to ganglion sphenopalatinum and from there centrally through the second branch of the V nerve. Schwartz and Weddell[39] have also supposed that the taste fibres were mainly carried through the great superficial petrosal nerve.

Lussana[25] supported by Lewis and Dandy[22] believed that the taste fibres were carried from the ganglion geniculi only by nervus intermedius (Wrisberg).

Ziehl[43] suggested still another pathway, namely by the route of the small petrosal superficial nerve to ganglion oticum and from there following the third branch of the V nerve.

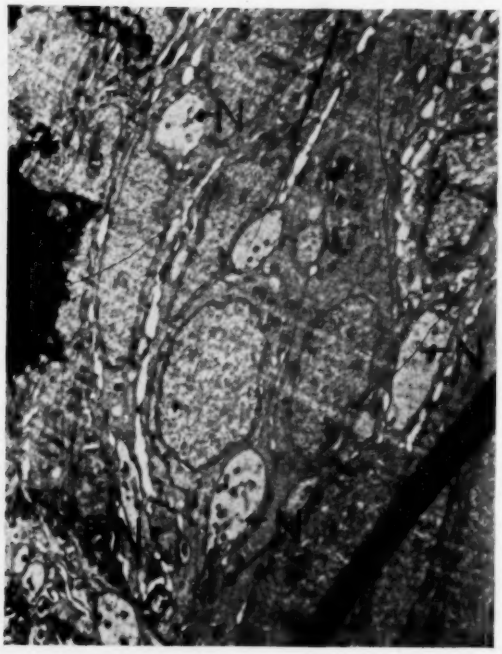

Fig. 6.—Lower part of a taste bud (guinea pig) with entering nerve fibres (EN) and intragemmal nerve fibres (N). These intragemmal nerve fibres are situated between the cells of the taste bud and contain mitochondria and "synapse granules." Electron microscopy: 6000x.

Eulenberg[10] and Landois[20] concluded that the taste fibres were carried by a communication between the geniculate ganglion and the IX nerve through the small superficial petrosal nerve, the tympanic plexus and Jacobson's nerve.

By recording the actions potentials it has been proved that stimuli by taste substances are transmitted through the chorda tympani.[44-46]

As to the peripheral course of the taste fibres it is, as stated above, according to Retzius, Kolmer and others, acknowledged that the nerve fibres at some distance from the taste buds lose their myelin sheath and enter the taste buds as intragemmal, unmyelinated fibres.

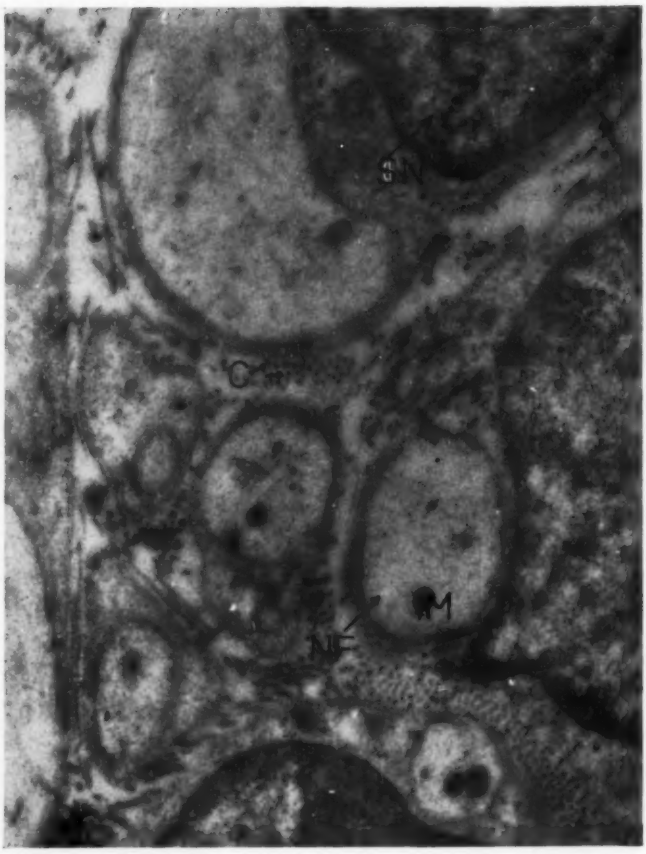

Fig. 7.—Cross sectioned nerve fibres (NF) just below the base of a taste bud (guinea pig). The nerve fibres have only a few layers of myelin. SN = nucleus of Schwann cell. Between the nerve fibres collagen fibres (C). M = mitochondria. Electron microscopy: 22000x.

In the structures below the taste buds a region is found which, from a morphological point of view, is very interesting. In this rather circumscript area a great number of nerve fibres shed their myelin sheath. It is often possible to find myelinated as well as unmyelinated nerve fibres in the same section. In that region where the multilayered myelinated nerve fibres lose their sheath the number of Schwann cells increase considerably and the small nerve branches are surrounded

Fig. 8.—Small ganglion below foliate papillae in the tongue of a rabbit. Silver impregnation according to Palmgren. Light microscopy.

by a layer of Schwann protoplasm and a few myelin lamellae. The diameter of the nerve fibres decreases considerably here and an increasing number of mitochondria appear. The nerve fibres enter the base of the taste buds as unmyelinated fibres and inside the buds they run an intercellular course. They can be followed comparatively high up in the taste buds, but we have never found them to reach the taste pore region. The diameter of the entering nerve fibres is small at the base, but between the different epithelial cells they often widen and

form clublike nerve endings. These nerve endings vary in size, but have in general the same structure. They contain a large number of slender mitochondrialike formations and rich amounts of small granules or rods with a diameter around 200-400Å. There is thus a striking resemblance to the so-called "synapse granules" as described in motor end-plates, retinal synapses and cochlear and vestibular nerve endings. Each clublike nerve ending is surrounded by a distinct membrane and nerve fibres entering epithelial cells have never been observed in our studies.

SUMMARY

In this paper a survey is given of the general structure of taste buds and peripheral taste fibres. The study has been carried out with light and electron microscopy. A series of micrographs are presented.

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The Scientific Papers of the American Laryngological Association

XXXI

HUMIDITY, A PROBLEM IN AIR-CONDITIONING

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It really *is* the humidity—as you may have heard—and not the heat. Since the advent of central heating it has been a bug-bear, which air-conditioning now aggravates in several respects. In the struggle between the nose and the machinery in the basement, sometimes the heater wins, and sometimes the cooler, but seldom the nose. When the doctor says to his patient, "Keep your living quarters reasonably humid in the winter months," it is likely that neither of them has a clear conception of what this entails or how ineffectual the attempt may be.

The importance of the respiratory mucous blanket has been so vigorously stressed that we may skip it and come quickly to the point. We deal here first with the water requirements of the mucosa; second, with the behavior of air-vapor mixtures at various temperatures; third, with certain characteristics of houses; and fourth, with the apparatus now available for controlling the humidity in a room.

REQUIREMENTS OF THE MUCOSA

The nasal mucus contains some 96 per cent water. To begin with, it is more viscous than mucus elsewhere in the body and even slight drying increases the viscosity enough to interfere with the work of the cilia. Demands on the nasal glands are great, even under usual conditions, and they cannot cope with extreme dryness indoors, in winter. Authorities differ as to the "comfort range" of temperature, however both physiologists and engineers regard it as closely approximating thermal equilibrium between the ambient atmosphere and the heat production and retention in the subject. Much of the

element of comfort has to do with the location, the season and the altitude, and with the subject's age, habits, occupation and clothing. For purposes of this discussion it will be regarded as ranging between 72°F and 74°F.

Optimum relative humidity for these temperatures has been variously given as 40 per cent to 45 per cent, and some tests with human subjects have placed it (with a temperature of 74°) as high as 79 per cent; but even the lower figures will be difficult to maintain in heated houses, as will appear.

Experience has shown that, with approaching winter, the first wave of dry-nose patients appears in the office when the relative humidity indoors falls to 25 per cent. It would seem, therefore that 35 per cent could be regarded as a passing grade, but 40 per cent as something to shoot at.

Every 24 hours the adult human breathes approximately 500 cu.ft. of air. In passing through the nose the air reaches a temperature of almost 98.6°F and a relative humidity of 95 per cent.

Five hundred cubic feet of air in this physiological state contains 1.2 pounds of water. Since this amount of air in a room at 72°F and .40 r.h. holds only .25 pounds water, then even under these ideal conditions the nose must supply daily .95 pounds—approximately a pint. With the humidity down to 20 per cent this becomes 1.08 pounds; at 12 per cent 1.125 pounds. But 500 cu.ft. in the warm lung was only 453 cu.ft. in the cool room at 72°, so that another 10 per cent must be added. However, some moisture from expired air is condensed on the turbinated bodies and re-breathed, partly cancelling this last.

It boils down to this: a pint of water is a lot of water for a small nose to turn out. In disease or old age it simply doesn't deliver; drainage stops and the germs take over.

Excessive humidity in the room is no parallel problem. The nose merely takes a rest. The skin is less fortunate, along with most of its contents.

MOISTURE PLUS AND MINUS

In terms of health and human working efficiency in the summer months humidity is the determining factor, and the wet, rather than the dry bulb reading is the index of tolerance.

According to figures of the United States Weather Bureau the average humidity of American cities in August ranges from 16 to 93 per cent but these figures are significant only as they are related to current temperatures.

In the so-called Temperate Zone—a misnomer, if ever there was one—there are many localities with high summer temperatures in the nineties and humidity around sixty-five per cent. In such climates dehumidification in homes and offices, and especially in theatres, stores and other crowded buildings is almost imperative. Unless the air is dried as well as cooled, perspiration fails to evaporate from skin and clothing and people shiver. In dry air evaporating perspiration does its own cooling and higher dry bulb room temperatures are tolerated with comfort. The removal of moisture is not too difficult. Air passing through chilled grids or cold water sprays loses its vapor by condensation.

The actual quantities of water involved in humidifying and dehumidifying are amazing—which is really what this paper is about.

The simplest unit with which we have to deal is a living room, or a bedroom or a sick room. A room 15 feet square, with a nine foot ceiling, contains approximately 2000 cu.ft.—a handy figure to refer to.

Private homes range from cottages without basement or attic, with a content of 6000 cu.ft., to spacious three story houses of 50,000 cu.ft. and more. Public buildings are individual problems; a ten-story office building will contain from 750,000 to 1 million cu.ft.

Take the large residence: in reducing the temperature in a 50M cu.ft. house from 90° to 76°, and the humidity from .65 to .40, 51.9 pounds of water must be got rid of: 26 quarts.

50M cu.ft. air (3500 lb. @ 90°) @ .65 r.h. contains	70	lb. water.
50M cu.ft. air (3650 lb. @ 76°) @ .40 r.h. contains	28.1	lb. water.
	51.9	lb. water.

I have checked the performance of an average refrigeration system in such a house, under the conditions referred to, and found the water being removed at the rate of six quarts an hour, which would do the job in four hours and twenty minutes, provided no fresh outside air came in.

TABLE I

Showing the effects upon the relative humidity of bringing the air to 72°F in January, in various localities:

PLACE	AV. JANUARY NOON TEMP.	AV. JANUARY P.M. REL. H.	REL. H. @ 72°F INDOORS
Chicago*	27	.74	.14
Cleveland*	30	.76	.16
Dallas	48	.62	.27
Denver*	38	.50	.18
Detroit*	27	.80	.14
Iowa City*	25	.75	.12
Los Angeles	62	.59	.40
Miami	73	.74	.76
Minneapolis*	15	.78	.08
New Orleans	59	.73	.47
New York*	34	.66	.18
Philadelphia*	37	.69	.19
Phoenix*	60	.38	.16
Portland, O.	42	.75	.26
St. Louis*	35	.69	.18
Salt Lake City*	33	.75	.17
Seattle	42	.79	.27
Washington, D.C.*	38	.64	.19
Waterville, Me.*	25	.69	.12

* Cities in which heating to 72°F depresses rel.hum. below 25%.

Not so simple is the addition of water in winter.

Let us select a mild winter day; the temperature is 30° and the humidity 40 per cent. One hundred cubic feet of air on this pleasant day carries approximately two ounces of water (0.134 lb.). Take it indoors, heat it to 74° and see what happens. The two ounces of water is still there but the 100 cu. ft. is now 109 cu. ft. and the 40 per cent humidity is now only 8 per cent. To bring it back to 40 per cent we must supply 1.2 ounces of water, which goes for every 100 cu.ft. in the house.

The 2000 cu.ft. bedroom will require a pint and a half; the 25,000 cu.ft. house two and one-third gallons; the 50,000 cu.ft. house four and two-thirds gallons: a sizable amount. If we are satisfied

with only thirty per cent the figures will be smaller, but not much, and this applies only to the *air* in the house. One reckons also with thirsty carpets, upholstery, draperies and woodwork which may double the amount—and all this on a *mild* winter day, with a barely freezing temperature. At lower temperatures the requirements pile up. What this amounts to in various parts of the country is shown in the accompanying table.

HUMIDIFIERS

To test the relative efficiency of some familiar humidifying devices a few careful measurements were made, not in the laboratory but under household conditions in sleeping quarters and sick-rooms. Tap water, and not distilled water, was used; doors, windows and vents were closed, but not hermetically sealed. Consequently there were minor errors which would not have been tolerated in a laboratory experiment, but the same variables occur in houses, and we do not sleep—most of us, that is—in our laboratories.

The amount of water evaporated per hour by the various contrivances is as follows:

TABLE II

	OZ. H_2O PER HR.
Tea kettle on gas flame	48-60
Cold water spray (centrifugal atomizer, furnace type, 25W)	21.03
Tea kettle on electric hot plate (600W)	19
Cold water spray, table type (70W)	16.5
Commercial steam vaporizer, standard make (250W)	10.5
Pan on radiator, per sq. ft.	1.0
Pan on table, per sq. ft.	.33

According to these figures the pint and a half required in the 2000 cu.ft. room would come from the tea kettle on the gas flame in 30 minutes; the same kettle on a hot plate in one hour, twenty minutes; the table spray in one hour, thirty minutes; and last, if not quite least, the commercial electric steamer in two hours, twenty-

four minutes. Pans of water, even on the radiator, are hardly worth mentioning.

Once the desired humidity has been reached replenishment must be constantly kept going because of losses through window cracks, chimneys, open doors and to an amazing extent even through brick walls when there is any wind. Efforts to humidify individual bedrooms are practically useless unless these losses are overcome by keeping the vaporizer going and what is more important, by keeping the room shut off from the rest of the house. In cold climates double window panes will be required if adequate humidity is to be maintained, otherwise condensation on windows will not only remove moisture from the air but water will run off and ruin the wallpaper.

To arrive at some figures, a bedroom was shut off by closing (but not sealing) doors, windows and registers. A table model centrifugal cold spray with a capacity of one pint an hour was put in continuous operation. At the end of two hours two doors were opened, one leading to a hall, the other to an adjoining room, with the following results:

HOUSE: brick, insulated.

ROOM: capacity 2100 cu.ft., 4 inside doors, 3 windows double panes, weather stripped, 4 vents closed.

OUTDOORS: dry bulb 49°F, wet bulb 38°F, .31 r.h., bar. 29.8 in.

HUMIDIFIER: cold centrifugal spray, capacity 16.5 oz. per hour.

TABLE III

TIME	DRY BULB	WET BULB	REL. H.
0:00	71	53	.27
1:00	69	53.5	.33
2:00	67.5	55.5	.44
	— 2 doors opened —		
2:10	70	54	.33
2:20	70.5	54	.32
2:25	72*	55	.31

* Between 0:00 and 2:25 house temperature rose from 71°F to 72°F

It required one hour, 30 minutes to raise the humidity only 13 per cent from a relatively acceptable 27 to a desirable 40; then, having risen to 44 per cent it fell back to 31 per cent only 25 minutes after the doors were opened, although the vaporizer was kept going. This is practically where it was at the start.

(The fall in room temperature during the first two hours was due partly to heat loss from evaporation and partly to radiation, the heating vents being closed and the outside temperature 49°.)

Fig. 1

Fig. 2

It has been contended that steam is superior to the cold spray in humidifying a sick-room because the evaporation from the latter reduces the room temperature whereas the hot steam device raises it. This is true but not of much consequence since the latent heat of water is the same whether the necessary Btu come from a furnace or a hot-plate. The furnace supplies them rather more economically.

A word regarding the furnace type centrifugal cold water spray listed in Table II: it is the successor in this residence plant to 1) an electrically heated water bath, 2) a pair of atomizer-type pressure sprays, 3) two moist-plate evaporators, 40 plates, 4) one home made large same. Of these the centrifugal spray was the most effective.

It has had to be abandoned, at least temporarily, because of one great draw-back: it scatters calcium dust all over the house, and

plays havoc with the nasal mucosa. City water contains solids in various amounts in various localities and until some practical and not too expensive means is found for filtering the dusts which develop on evaporation from cold sprays this type of spray leaves something to be desired. Ordinary furnace filters are only partly effective.

The following figures are indicative of the amount of solid matter in city water in several communities. They were kindly supplied by the water commissioners of those cities.

TABLE IV

	TOTAL SOLIDS, PARTS PER MILLION
Boston	43
Chicago	154
	159
	199
	165
Denver	104
Miami	105
	177
Minneapolis	126
Philadelphia	250
	133
St. Louis	298

In grains per gallon this ranges from 2.5 to 17 gr.

Assuming an average solid content of, say, 10 grains per gallon the 50,000 cu.ft. house would receive some 420 grains of white powder every week. In St. Louis it would come to almost an ounce and a half; in Boston only one-seventh as much. Dust gathered from furniture and parts of the heating system was found to contain chiefly calcium and magnesium salts, in both amorphous and finely crystalline form (Fig. 1). Adding a drop of water to the dust on a microscope slide, and allowing the preparation to evaporate slowly, brings out the characteristics of the crystals (Fig. 2).

A final observation on humidity indicators: the sling psychrometer is the instrument of choice for use in the home. Dial instruments

depending upon the expansion and contraction of a thread of sensitive material under the influence of moisture are not very accurate. A strip of paper with graduated spots of cobaltous chloride, which turn color successively with changes in moisture is consistent over all, if not precise. Stationary wet and dry bulb thermometers are singularly misleading even under a reasonable amount of fanning.

Five instruments were tested against one another just as they came from the shop:

TABLE V

	HUMIDITY READING	ERROR
Sling psychrometer	.26	
Wet and dry bulb, stationary	.545	+28
Wet and dry bulb after fanning	.39	+13
Commercial dial type	.22	— 4
DeLuxe dial type	.31	+ 5
Dial type (advertising novelty)	.37	+11

The adjustable dial instruments were then set to conform to the psychrometer reading and the next day the results were a little worse: −6, +6 and +11 respectively.

From all these dull figures one may gather that the control of humidity in the house is not simple. The fellow with gadgets and contraptions on his furnace is better off than the one with pans of water on the radiator but maybe not so much as he thinks.

Medical programs are packed with brilliant last words on every subject from broad-spectrum antibiotics to the sines and cosines of the nasal angles while here I stand still wondering how to moisten a house. It may be just fortunate that no solution is at hand, for when the solution is found the mid-winter crush in your office and mine will be at an end.

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XXXII

HISTAMINE-RELEASING DRUGS

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In recent years observations upon the release of tissue histamine by drugs have been multiplying rather rapidly. Such observations are of interest from a number of points of view. First, because they throw light on some of the side-effects—expected or unexpected, and usually unwanted—that accompany the therapeutic effect for which the drug is given. Secondly, because they afford a new approach to the old problem, the part that histamine plays in the body's normal economy; for it is unfortunately true that in spite of much research the physiological role of this powerful and ubiquitous substance is a matter more of speculation than of knowledge. Thirdly, there is the hope that, since histamine release is undoubtedly a component of certain pathological reactions, especially allergic reactions, we might use histamine releasers to find out more about these phenomena. And lastly, there is the possibility that the pharmacological release of histamine might in some circumstances be useful in therapy. Progress along these various lines has hardly been spectacular; but some of the outlines of the picture are beginning to stand out and a few of the details have been clarified.

Before I discuss the histamine liberators it may be useful to recall some points about the location and action of histamine itself.

As to the distribution[1] of histamine in the organism, most of our information comes from animals; but combining this with the rather scanty data on human tissues it seems safe to guess that the human body contains several hundred milligrams of it, an amount which would certainly produce a very severe reaction or even death if it were all let loose at once. Practically every tissue that has been examined contains measurable amounts; the concentration varies however not only from tissue to tissue, but also from one individual to another. Mucous and serous membranes are often particularly rich in histamine, and substantial amounts are also found in association with striated and smooth muscle and in skin and subcutaneous tissue.

There is no striking sex difference, but in some organs the concentration appears to increase with age. The recent works of Riley and West[2] in Scotland and of Graham and her co-workers[3] in St. Louis have shown beyond any doubt that a great deal of this stored tissue histamine is located in a particular kind of cellular element, the mast cells. These large granular cells were first recognized by Ehrlich[4] because of their affinity for basic dyes, some of which like toluidine blue stain them metachromatically. Metachromasia, as we now know, is characteristic of acidic substances of high molecular weight, particularly sulphated polysaccharides. The strongest naturally occurring acid of this group is heparin; and a group of Swedish workers[5,6] under the leadership of Jorpes showed, about twenty years ago, that heparin is located in the mast cells and accounts for their characteristic staining properties. Riley and West have shown that there is a close correlation between the mast-cell content of a tissue and its histamine content, the most striking example perhaps being the mast-cell tumors occasionally found in elderly dogs, which may contain up to 1 per cent of their dry weight as histamine. Graham and her colleagues have likewise shown that the blood basophils, which may be regarded as circulating mast cells, have a very high histamine content. Histamine and heparin thus inhabit the same cell, a finding that makes sense of many old observations. For instance in anaphylactic shock in the dog the arterial pressure falls catastrophically, and the blood becomes incoagulable: there is enough free histamine in the blood to account for the circulatory effects, and enough free heparin to account for the absence of clotting. The histamine and heparin have come at least in large part from the mast cells, which in many tissues, especially the liver, are found to have been disrupted. Quite recently another powerful substance, 5-hydroxytryptamine or serotonin, has been found in mast cells.[7]

The mast cells, however, are not the whole of the histamine story. The platelets of rabbit blood and the neutrophil leucocytes of human blood contain stored histamine, and it seems highly probable that there is also a good deal in smooth muscle cells and gland cells, that is to say, in cells which are often themselves very sensitive to free histamine.

The actions of histamine fall into three main groups. Most smooth muscle is contracted, and this is true of smooth muscle of the large and medium-sized blood vessels in most mammals. The smallest arterioles and the precapillary sphincters, on the other hand, are

relaxed in man and the carnivores, so that the over-all effect is vasodilatation unless the local concentration of histamine is high enough to cause spasm of the larger arteries. Gland cells are usually made to secrete, the parietal cells of the stomach being particularly sensitive. Finally, capillary permeability is increased, almost certainly by a direct action on the intercellular cement substance, so that the capillary wall becomes much leakier for plasma protein. Most of these actions are opposed more or less effectively by the antihistamine drugs (the effect on the gastric glands being an exception). If, however, the local concentration of histamine is very high, a correspondingly high concentration of antihistamine will be needed, and this cannot usually be attained when the drug is administered by one of the usual routes. Thus the failure of antihistaminic therapy to prevent an allergic response, for example, does not necessarily mean that the response was not mediated by the release of histamine. The histamine may have been released so close to its site of action that enormous doses of antihistamine would be required to antagonize it.[8-10] In general it appears that the effects of histamine-releasing drugs, if not too great, can be prevented by antihistamines if the dose is sufficiently increased, and that the effects of antigens on sensitized tissues are harder to protect against. But the situation is complicated by the fact that not only are the antihistaminics rather unspecific in high dosage, but they are themselves histamine releasers.[11-13] I do not mean to imply here that antihistamine-resistant allergic phenomena are always mediated by histamine. That certainly would be untrue: besides heparin and serotonin a good many other active substances, including various enzymes and polypeptides, are mobilized or activated in allergic reactions.

We may now focus our attention more directly on drugs that liberate histamine. It has been known for some time that a variety of materials like protein precipitants, proteolytic enzymes and the venoms of snakes and bees have this effect. That this is so is not surprising, since such substances are nonspecific poisons that damage a wide variety of cells. It has also been known for a long time that hydrolyzed protein in the form of Witte's peptone produces in the dog effects remarkably like those of anaphylaxis; and during the thirties it was shown, by Dragstedt[14] and Wilander[6] respectively, that both histamine and heparin are released in peptone shock. The first well-defined chemical compounds shown to be histamine releasers were, however, the curare alkaloids, whose effect was discovered in 1939 by Anrep and his collab-

orators in Egypt, in the course of a research with quite a different aim. In 1947 Schild and Gregory[15] showed that strychnine and the related alkaloids can release histamine, and Paton and I[16] made a similar observation with licheniformin, a polypeptide antibiotic. Licheniformin was particularly interesting to us since it seemed to have little toxicity apart from its ability to release histamine. We discovered its activity in a roundabout way. When injected into a cat or dog whose blood pressure was being recorded it produced a kind of effect we had not seen before: at first nothing happened at all, but after about 20 seconds the pressure fell precipitously. Analyzing this phenomenon, we found that blood samples taken after the pressure had fallen produced, on injection into another animal, not a delayed but an immediate fall of blood pressure; and we found that this rapid effect was due to the presence of free histamine in the blood. We thought we ought to look for other substances that acted in this way. The chemical structure of licheniformin had not been worked out in detail, but it was known to give a color reaction for the basic guanidine grouping, so we tried a compound called synthalin which is a guanidine derivative and happened to be on the laboratory shelf. Synthalin produced just the same sort of delayed depressor response we had seen with licheniformin, and proved also to be a histamine releaser. With this clue we tested a great number of compounds of related chemical structure, among which we found several dozen with the type of action we were looking for. Among them was one class of therapeutically useful compounds, the diamidines, stilbamidine, pentamidine and their relatives, which had been widely used in Africa for their trypanocidal properties, and we were interested to learn that their side-effects in man, when given by vein, include "a severe but transient fall in blood pressure . . . a curious puffy suffusion of the face and eyelids . . . and itching, generalized and often very pronounced, the grotesque antics of the patient, trying to scratch every part of his body simultaneously, being a source of great amusement to his companions."[17] There seems to be no doubt that these side-effects are due to histamine release. The therapeutic action of the drug, of course, depends on what it does to the parasite, not on what it does to the host.

All these compounds produced similar effects in a variety of tests. In the dog they released heparin along with histamine, but in the cat, only histamine was released. The histamine released in the dog came mainly from the liver, but in the cat it came mainly from skin and muscle. The released histamine, besides acting on the ves-

sels, constricted the bronchi, stimulated gastric secretion, and so on. Minute doses injected intradermally in man produced the wheal-and-flare response characteristic of histamine. Rodents like the mouse and rat, which are insensitive to histamine, could tolerate relatively large doses of the liberators.

Chemically the compounds we studied were all bases. Those that produced a "clean" effect (i.e., that had no obvious immediate action that could not be ascribed to the histamine they set free) had a rather characteristic kind of chemical structure. They had the general formula RXY, where R was a basic group (amino, amidino, quaternary nitrogen, etc.); Y was another water-soluble group, not necessarily basic, at the far end of the molecule, and X was a sizeable moiety, not too big or small, of predominantly hydrocarbon structure. The addition of water-soluble groups elsewhere in the molecule either reduced the potency or superimposed activity of a different kind on the histamine-releasing activity. This general formula includes a large number of drugs, but it now appears to be much too restricted. Almost any organic base given in sufficient dosage will release histamine; the simplest aliphatic monoamines,[18] and even ammonia,[19] are fairly potent, though they seem less specific and explosive in their action than, say, the diamines or diamidines. Histamine release is also a feature of the toxic action of bile salts[12] and of certain nonbasic detergents,[20] and in rodents it is produced by rather small doses of the plasma substitutes dextran and PVP,[21] which are nearly nontoxic to man and the carnivores.

The relative potency of histamine liberators covers a wide range, and differs greatly according to the test object on which they are compared.[22] Collier and Macauley[23] suggest that for the evaluation of histamine-releasing potency in man, the whealing activity in human skin may be the best guide. By this and several other tests the most active (and one of the most specific) liberators is compound 48/80, a polybasic aromatic substance whose remarkable activity was first observed by Paton.[24] A molecule of this substance under the most favorable conditions will release more than ten molecules of histamine from the skin.

The effects of histamine liberators in man have received remarkably little study. The side-effects of the diamidines have already been mentioned and incidental observations suggestive of histamine release have been made with many other drugs known to possess this action in animals. Recently Lecomte[25] has given substantial doses of a

new histamine liberator, 1935L, to human volunteers. In addition to the effects already mentioned, he noted erythema limited to the face and upper trunk and headache; the clinical aspect was that of angioneurotic edema. The effects were transient, were only seen when the injection was made quickly, were partly annulled by antihistaminics, and diminished with each repetition of the dose.

The established drugs that have been shown to release significant amounts of histamine include those on the following list (modified slightly from Paton[26]).

Quaternary salts	d-Tubocurarine
	Mytolon
	Synthetic quaternaries related to the methonium series
Morphine alkaloids	Morphine
	Codeine
	Papaverine
Other alkaloids	Atropine
	Scopolamine
	Quinine
	Dihydroergotamine
Chemotherapeutic agents	Neoarsphenamine
	Propamidine
	Pentamidine
	Stilbamidine
	Antrycide
Circulatory drugs	Apresoline
	Priscol
Sympathomimetic agents	Amphetamine
	Tyramine
Centrally acting drugs	Demerol
	Strychnine
	Amphetamine
Antihistamines	(Various)
Protein hydrolysates	
Protamines	
Basic amino acids	

The list is certainly incomplete, and no doubt could be greatly extended by anyone interested enough to do a systematic investigation. Indeed it is likely that any basic drug (and probably half of any list of useful drugs would turn out to be organic bases) will release histamine when given in sufficient dosage. This naturally does not mean that effects ascribable to histamine will be seen whenever one of these drugs is given. When a drug has a powerful specific effect, its subsidiary effects may be neglected, including histamine release unless it is a highly potent liberator. Histamine release in unusually susceptible subjects may, however, be at the root of certain "drug allergies," including vascular collapse, nitritoid attacks, urticaria, etc. These effects, it must be stressed, may be produced without previous sensitization to the drug. It is also easy to think of some minor features of the action of certain common drugs that may involve the same mechanism: such are the poor tolerance of asthmatics for morphine and the itching sometimes seen after that drug, and the flushing of the upper part of the body sometimes produced by atropine.

How and where do the histamine liberators act? Probably mainly or entirely on mast cells; they seem to have little direct action on organs like the intestine, which is sensitive to histamine but whose rich stores of this base are for the most part not located in mast cells. Those who are interested in the details of the mechanism may refer to the numerous papers dealing with this subject in the recent Ciba Symposium. It seems clear that the histamine and heparin of the mast cells is located in intracellular particles. These particles can be isolated by differential centrifugation of tissue homogenates, and their behavior in the presence of histamine liberators can then be studied.[27-30] My colleagues and I[29,31] are attracted by the hypothesis that basic drugs are accumulated within the mast cells by virtue of their affinity for the heparin stored there; when a sufficient concentration has been reached, the histamine-containing granules are lysed or become freely permeable for histamine, or the lytic action may extend to the cell membrane itself. The heparin of the mast cells is also released, but most of it is trapped by the tissues and fails to reach the blood stream.

What is the relationship between the allergic or anaphylactic release of histamine and the release of histamine by drugs? The answer to this question is not clear. In some tissues at least the released histamine comes from the same store, in the mast cells apparently, whatever the mechanism of release. The histamine stores of rat skin

can be almost entirely depleted of histamine by repeated dosage with a histamine liberator,[32] the skin replenishes its histamine only over days or weeks, but remains healthy in appearance and shows normal passive anaphylactic reactions with an antigen to which it is sensitive.[33] It would be tempting to suppose that in the allergic reactions the antigen-antibody reaction triggered some enzymic reaction leading to the formation of basic or polypeptide histamine liberators. But experiments aimed at detecting such a process have so far given only negative results; and, as already pointed out, in some tissues the anaphylactic reaction appears to be independent of the presence of mast cells. It is conceivable that by the local application of a histamine-liberator, a sensitized tissue could be depleted of its histamine stores for a long period, for instance the season for a particular pollen: the antigen-antibody reaction to the allergen would then still take place, but would have fewer unpleasant consequences. The sudden unloading of the histamine depots would produce a severe reaction, but this could presumably be controlled with antihistamines and adrenalin. The idea of using histamine liberators in conditions where a prolonged histamine effect is required, as in Ménière's disease, appears rather unpromising because of the steepness of the dose-response curve with these substances and the brief action of the released histamine. At present the chief interest of these substances lies in their usefulness as research tools and in the light they throw on the subsidiary actions of a number of useful drugs.

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XXXIII

OTOLARYNGOLOGIC ASPECTS OF HYPOMETABOLISM

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The essential regulator of cellular oxidation is a catalytic agent—the thyroid hormone. Normal cell metabolism cannot proceed in its absence. This is true for all the cells in the body.[1] This essential substance is probably in its circulating phase, levothyroxin loosely associated with plasma proteins.[2-4] It is the mobile portion of thyroglobulin[5]—the protein-hormone combine formed by the secreting cells of the thyroid gland and stored in the acini of the gland. The hormone is moved from its storage depot in the gland into the blood stream where it is conveyed to every living cell in the body. It is possible that the fourth iodine atom of thyroxin is spent by degradation process and that triiodothyronine is the transient substance immediately effective at cell level. The mobilization of thyroxin from the thyroid gland is effected by the thyrotropic hormone of the anterior lobe of the pituitary gland. The quantitive release of thyrotropic hormone from the pituitary is influenced by the level of the thyroid hormone in the blood and probably by the level of other hormones as well—notably those from the adrenal cortex.[6] A normal blood level of thyroid hormone, in turn, is necessary for the normal functioning of all the endocrine glands.

The circular chain-like action from pituitary to thyroid and back to pituitary is not independent and self-serving, however. Evidence in recent years demonstrates the commanding influence of basal nuclear aggregates in the anterior hypothalamus over pituitary thyrotropin secretion.[7,8] In any case, the final essential in this sequence is the presence of an adequate level of free thyroxin in the plasma. As stated, it circulates principally in a loose association with plasma proteins[9] and may break down to triiodothyronine before it affects the cell. The cellular phase of metabolism in which thyroxin facilitates oxidation in the individual cell is relatively unexplored.[10] It is reasonable to assume that dysfunctions exist even at this peripheral stage.

Hypometabolism as a systemic problem can result from impaired function at any level in the chain. Four etiologic forms have been

postulated:[11] 1) hypothalamic, 2) pituitary, 3) athyreotic, 4) somatic or peripheral. The advanced degree of athyreotic hypometabolism causing widespread mucoproteinous changes in the tissue ground substance is commonly called myxedema. This is but one form and one degree of hypometabolism. Hypothyroidism denotes a state of thyroxin insufficiency in the tissue cells. In this sense it coincides with the clinical state of hypometabolism. Hypometabolism is a common clinical condition. Myxedema is relatively uncommon.

Hypometabolism is characterized by a wide range of nonspecific symptoms headed by fatiguability and cold intolerance. It is probably true that no organ is immune to the lowered tone of this semivegetative metabolic state. The symptoms evoked make for a complaining, unwell patient readily buried in the psychoneurotic index. Coarse hair, thick skin, infertility, sluggish mentality, and bradycardia may be uniformly indicative of severe hypometabolism. Unfocalized symptoms like constipation, headache, arthralgia, chronic fatigue, fleeting sensory disturbances, transient swellings of face or ankles and others may individually or in various combinations suggest moderate hypometabolism.

DIAGNOSTIC METHODS

Starr[12] suggests that the specific diagnosis of hypothyroidism is best made by determining the level of the serum protein bound iodine. It may be presumed that this is made up almost entirely of the circulating thyroid hormone. The normal human level ranges from 4 to 8 micrograms per cent. The hypothyroid range extends downward from 3.8 micrograms of protein bound iodine per cent. This precise determination avoids the many pitfalls of the basal metabolism test and is applicable where the latter is not—as in children, respiratory and cardiac patients and others unwilling or unable to co-operate. This chemical method is useful not only as a determinant of thyroid function but as a gauge of therapy as well. Its limitations are principally those of availability. Many laboratories do not maintain the facility. This, however, is a question of demand.

It is true that the measurement of heat produced in the process of cellular oxidation is a true measure of the metabolic activity of an organism. The amount of oxygen used to produce the heat is an indirect gauge of the latter. A standard range of normal at basal conditions exists for the human body. Application of this standard in clinical practice is uncertain because it is difficult to attain and maintain basal conditions for the duration of a test period. The admitted inaccuracy of approximately fifty per cent of basal metabolic determinations is the result. Most of the inaccuracies result in eleva-

tion of the range above the patient's true normal. For this reason a reported low rate can be accepted as true hypometabolism. The high side errors exclude many hypometabolics from correct diagnosis, however.

The radioactive iodine (I^{131}) uptake of the thyroid gland is probably the simplest of the radioactive iodine methods of estimating thyroid function. The uptake, a specific interval after ingestion of 15 to 25 microcuries of I^{131}, is measured with suitable apparatus and techniques. The usual interval is 24 hours though this has been modified downward to as little as six hours. In the 24 hour method results are said to be 80 to 85 per cent accurate in their relation to the true thyroid function.[4] Uptake values of 55 per cent or higher are indicative of hyperthyroidism. Values of five per cent and below show the presence of hypothyroidism.[1] The zone from five to ten per cent is suspect.

The use of iodides and thyroid decreases radioactive iodine values as long as six weeks after discontinuance. Estrogens, cortisone and other steroids can also decrease the uptake of the thyroid. Presumably this is effected through pituitary inhibition. False low values may be obtained under these circumstances. Conversely in hypopituitary hypothyroidism uptake values may be in the low normal range and the diagnosis thereby missed.

In most instances the uptake of radioactive iodine and its release from the thyroid gland as hormone run parallel. There are circumstances where there is divergence. In such instances the uptake value does not indicate the quantity of circulating hormone. The measurement of protein bound radioactive iodine (hormone) in the blood a fixed interval after ingestion, or the measurement of the rate at which it appears in the plasma should therefore be a more accurate indicator of hormonal status than the uptake determination. Unfortunately, these plasma methods do not distinguish between the euthyroid and the hypothyroid satisfactorily.

From the foregoing it is apparent that in the laboratory aids to the diagnosis of hypothyroidism there is room for improvement. The basal metabolic rate method is useful in diagnosing hypometabolism. Unfortunately, it commonly errs to the high side. The radio iodine methods may falsely imply a euthyroid to be low and a hypothyroid to be normal. The chemical determination of the protein-bound iodine of the plasma is the most certain method. Second in value and often useful for confirmation is a properly performed basal metabolic rate determination.

Diagnosis by therapeutic test with thyroid substance is not very satisfying. Hypometabolism is clinically vague and deceiving. A

level of hormonal adequacy is not built up over night. Medication has to be persisted with and often increased gradually over long periods of time to obtain optimal results. All of this is difficult to persevere with on a "hunch" indication alone. The price of unrecognized hypometabolism in our field is long-standing disability and sometimes, irreversible pathology. Preventive therapy must be long term, sometimes life-long. Therefore a firmly based diagnosis rather than a presumption should be made at the outset.

HYPOMETABOLISM IN OTOLARYNGOLOGY

In otolaryngology hypometabolism is a frequent cause of presenting symptoms.[13,14] The otolaryngologist has an excellent opportunity to recognize it. The larynx, the upper respiratory mucosa, the external and middle ear, the pharynx, the cranial vessels, or the inner ear may be the focal point of symptoms.

THE LARYNX

Chronic vocal cord edema not associated with inflammatory reaction is strongly suggestive of hypothyroidism. It is firm, not deeply reddened unless it bears the brunt of excessive vocal trauma, and it is uniform in its involvement of the whole cord. Because of greatly increased cordal thickness the voice is hoarse and of low pitch. Most patients with myxedema grade of hypothyroidism have a low, coarse voice. Advanced degrees of cordal myxedema may result in diffuse polypoid change requiring surgical stripping. The gelatinous character of the submucosa due to the mucoproteinous change in the tissue ground substance makes separation of the edematous masses from the underlying elastic tissues of the cord relatively easy with the usual cupped forceps technique. The focalized myxedema and polyps will recur if the hypothyroidism is unsuspected and untreated.

REPORT OF A CASE

Mrs. C.S., a white female aged 64, was examined on May 25, 1953. She had been hoarse for more than a year. The hoarseness fluctuated in degree from week to week but was always quite severe. Diagnosis of vocal cord polyps had been made by a competent laryngologist in a distant part of the country some months before. It was his suggestion that the polyps be removed forthwith.

The patient was chronically beset with great fatiguability and cold intolerance. She had a very apparent fluid-holding tendency. There was loose, pouchy edema of the lids. Puffiness of the fingers resulted in indentations from her rings. Her ankles and feet were edematous. Both vocal cords were edematous in the extreme with their medial aspect tensely polypoid.

The patient's internist agreed with the tentative diagnosis of severe hypothryoidism. He found her also to be moderately hypertensive.

The basal metabolic rate proved to be minus 27 per cent. In an apprehensive patient who accommodated to her test inconveniences with less equanimity than was perfectly desirable this was a very significant figure since it probably erred on the high side.

In the course of the next three months with thyroid replacement the patient lost a great deal of fluid and face and extremities took on a healthy tissue appearance. The vocal cord mucosa was loose and floppy along the whole free margin. Though much of the edema was gone there was insufficient elasticity in the membrane to return the lining to normal tonus. To a more limited degree this was also true of the pouchy skin of the lower lids. Her maintenance dose of dessicated thyroid levelled optimally at 2½ grains a day.

Not until June 13, 1955, did the patient pause in her worldly wanderings sufficiently long to have the vocal cords stripped. Healing thereafter was prompt and her laryngeal function and appearance have remained good.

Bilateral vocal cord paralysis is caused most frequently by extensive thyroid surgery. A thyroid excision that involves both recurrent laryngeal nerves is likely to be so complete that hypothyroidism results. Protein-bound iodine measurements or radioactive iodine studies are indispensable to this diagnosis. The respiratory apparatus of the metabolometer is not usually applicable to the obstructed or tracheotomized patient.

The respiratory obstruction due to median vocal cord position can be significantly increased by the mucoid edema of the cordal mucosa. The airway can be improved measurably by restoring the normal mucosa with thyroid replacement. This is partially offset by the increased respiratory demand of the improved metabolic state.

REPORT OF A CASE

Mr. R.D., a 69 year old white male, was examined on February 25, 1955. His history was interesting. In September 1954 he had a near total thyroidectomy for multiple-adenomatous goiter. A few hours postoperatively an emergency tracheotomy was performed because the patient's condition had deteriorated due to respiratory obstruction, the gravity of which had not been adequately appreciated at the conclusion of surgery. Several efforts were made in October, November and December, 1954, to decannulate this patient without first visualizing his larynx. They were nearly disastrous. In January, 1955, the patient complained of buzzing and roaring in his ears and of fluctuating hearing level. At this time he also had a period in which he had hallucinations and "heard voices." Throughout the winter months he had cold intolerance and increasingly slow cerebration.

The patient's whole physical appearance was that of well established myxedema. A tracheotomy tube was present in high position. Both vocal cords were immobile in the midline. There was firm edema of both arytenoid and ventricular mucosal areas with a reddened inflammatory appearance on the right side. The vocal cords were immobile and in the midline and it was difficult to visualize their whole length because of the edematous supraglottic mucosal overhang. His tongue was thick and clumsy. The upper respiratory and pharyngeal mucosa was thick and edematous. There was bilateral hearing impairment with a sharply downsliding audiographic tracing from the 20 decibel level at the frequency 512 to 80 decibels at 4096.

The radio-iodine uptake was 2.3 per cent and the conversion to protein-bound (plasma hormonal) iodine was low. The interpretation was myxedema level.

One-half grain of dessicated thyroid daily for a week was given and produced no sign of cardiac overload so increase was made to one grain daily.

Preoperative preparation demanded long term replacement to attain optimal metabolic tissue rejuvenation. However, the high position of the tracheotomy tube and reaction in the right cricoarytenoid area were disturbing evidence that cricoid perichondritis was in process. Accordingly laryngoplasty and tracheotomy were effected on March 4, 1955. The cricoid had been violated by the initial "laryngotomy." This area was repaired, the trachea brought from beneath the sternum by traction, and tracheal tube inserted through the second ring.

The soft tissues exposed in this surgical effort were pale and edematous and gave forth a myxomatous ooze when incised. Healing time was very prolonged.

By mid-April, 1955, enough laryngeal edema had cleared that visualization was better. The left vocal cord had sufficient motion to swing past the midline and phonate against the immobile right cord. The left vocal cord had poor abduction power, however. Immediately subcordal there appeared to be a semistenosing bar presumably as a result of the laryngostomy chondritis.

This patient's myxedema is now well controlled. As with most myxedema patients four grains of dessicated thyroid per day caused gradual signs of hyperthyroidism which were unrecognized until auricular fibrillation developed. His family doctor downgraded his overdose to a maintenance level of two grains per day. His physical well being is "normal." For average activity he can keep his tracheotomy tube completely taped. Decannulation has not been done because his previous occupation called for physical exertion beyond average. At present he is determining his obstructive threshold with a full daily work load. It is probable his right vocal cord will need lateral displacement.

Hypothyroid tissues heal poorly. The normal character of the processes of wound healing are grossly altered. To those who have incised the soft tissues of the myxedematous patient this is not new. One does not forget the mucoid character of the interstitial fluid ooze. To preclude delayed healing after arytenoid surgery the thyroid status should be determined beforehand and the necessary preoperative weeks be invested in establishing normal metabolic balance. For the hypothyroid patient controlled with replacement therapy, the satisfaction of arytenoid surgery and decannulation can be nullified by a relapse into the hypothyroid state. The return of mucoid edema at the glottic level can revert the postsurgical adequate airway to a condition of respiratory embarrassment. It is difficult for some patients to see the necessity for continuous thyroid therapy. Their sense of well-being when in normal balance suggests that they are too well to be taking medicines. The price of the lapse is not paid for several months. By that time developing symptoms are not associated with lack of a medication long since discontinued. For the patient with an adequate airway and a good voice following arytenoid surgery the gradual return of laryngeal myxedema can vitiate the result.

THE NOSE

Mucoproteinous edema of the nasal mucosa is productive of chronic nasal obstruction. A change in the character of the nasal secretions to a more tenacious and mucoid quality creates the additional annoyance of postnasal accumulation. Enough has been said and written of the problem to alert the specialty to its occurrence.[15] It only takes a case refractory to prolonged nasal piddling, surgery, and allergic management but spectacularly responsive to adequate thyroid replacement to enlighten the clinician and broaden his concepts. The patient is usually as grateful for the systemic benefits as for those nasal. His improved vigor, bowel tonus, cold tolerance, arthralgia, etc. when analyzed in retrospect embed these important accessory data in future diagnostic questioning. The frailties of a specialized history are principally those of narrow vision.

REPORT OF A CASE

Mr. S.V., a 36 year old male, was first examined in November, 1953. For over five years he had had persistent, severe nasal obstruction and mucoid, tenacious postnasal drainage. His symptoms were always worse in the wintertime. He had had frequent local nasal treatments of various types much of that time. He had a well-developed Privine habit, and used the drops particularly frequently at night. Two months before examination he had a left upper molar tooth removed and coincident with this or subsequent to it he developed an acute suppurative left maxillary sinusitis. His family physician gave him penicillin by injection.

At the time of examination there was no residual suppuration but edema of the left maxillary sinus mucosa was still present. The rest of the sinuses were clear and normal. The nasal mucosa was exceedingly edematous, pale and wet. It showed very little decongestant response to 2 per cent ephedrine solution. In the week between initial examination and appointment for basal metabolic rate determination there was no significant response to antihistaminics. Basal metabolic rate was reported minus 36 per cent and the blood cholesterol 187 mg per cent. There was slow gradual improvement in the next three months as the daily dose of dessicated thyroid was increased from one-half grain daily to one and one-half grains daily. The latter dose is an optimal daily dose for the patient and has maintained complete nasal comfort regardless of season, for the past two years.

THE EXTERNAL AND MIDDLE EAR

One of the usual symptoms of hypothyroidism is a reduction of sweat gland activity. Frequently the function of ceruminous glands suffers the same fate. The dry, itching external ear which results is a frustrating problem unless the diagnosis of thyroid deficiency is made. Improvement is not obtained with local treatment.

This would be a simplified clinical world if some of our vexing chronic or recurrent problems were demonstrated to have single or specific etiologies. Response to a single "standard" treatment could then be expected. If, for example, chronic auditory salpingitis and

effusive otitis media would respond to the empiricism of nasopharyngeal irradiation with uniform and lasting results we might be spared the necessity of making an etiologic diagnosis. After the initial flush of irradiation enthusiasm we are returned to the arduous requisite of the diagnosis first. One suspects the dermatologist came to grips with the same harsh reality in his effort to control a rambling range of dermatitides with superficial irradiation.

Some effusive ears are bettered by good allergic management and some by thorough nasopharyngeal surgery and middle ear aspiration. But some have long-standing betterment from nothing at all except correction of a chronic thyroid deficiency.[16] In many of these, concomitant lymphoid hyperplasia can be permanently controlled with adequate thyroid replacement. This is the same lymphoid hyperplasia which defies repeated and adequate removal.

REPORT OF A CASE

E.W., a white male aged nine years, was examined on January 28, 1948. He had a chronic problem with nasal obstruction and mucoid drainage in excessive amounts which had no seasonal pattern. It was his parent's impression that he had a hearing handicap of long standing.

This boy had had tonsillectomy and adenoidectomy performed by his pediatrician three years before.

Juicy, edematous mucosa was the outstanding feature in the nose and nasopharynx. There was diffuse lymphoid hyperplasia centrally in the nasopharynx, in the tubal area and downward into the lateral pharynx. There was effusion in both middle ears and hearing impairment averaging 20 to 30 decibels in a flat tracing for both ears.

This boy was referred for consideration of nasopharyngeal irradiation and I, myopic clinician, concurred. On three occasions at the usually recommended three week intervals the usual 50 milligram nasopharyngeal applicator was placed over the tubal area for the usual twelve minutes to the side. In addition the patient was placed on a diet restricting several of the commoner food allergens.

Three months after the initial examination and treatment the middle ears were ventilating well, hearing was normal and there was diminution in the mucosal edema in the nasopharynx.

A year later the hearing was still almost normal, but the patient's mother was unhappy with his chronic nasal behavior which was diagnosed chronic vasomotor rhinitis. She was advised to bear with it lest the indicated vasomotor or allergic regime be not more troublesome than the disease.

On several subsequent occasions the mother expressed distress with the chronic nasal symptoms and was certain that intermittently the patient had periods of hearing impairment.

By February 28, 1956, the patient—having survived all of the above—was of an age (18 years) to speak for himself. He had had two miserable winters with his nose. The summers had been reasonably comfortable. In spite of the extensive background on our records he volunteered that two years was as long in retrospect as he could recall any nasal problems.

There was no question but that this patient's complaints were justified. His nasal mucosa was juicily edematous to an advanced degree. He breathed through his mouth as a matter of habit and necessity.

There was no ring of true allergy to the problem. There was no additional information gleaned from the history as he gave it. Arbitrarily he was referred for radio-iodine study. His uptake was 8.3 per cent. His conversion to circulating hormone was low. He became asymptomatic in a month with a daily dose of one grain of dessicated thyroid.

At this point this patient's history was pursued further with direct questioning of his mother relative to thyroid deficiency. The fallibility of history-taking and the wisdom of maintaining thyroid-consciousness in our specialty at all ages became evident. At the age of nine months an astute pediatrician diagnosed thyroid deficiency and bettered the infant with replacement therapy. It was later discontinued, presumably through indifference and well-being. The same pediatrician referred him for care and irradiation at the age of 11 years when his nasopharynx became a focal point of distress and recurrent lymphoid hyperplasia. The key to long-standing therapeutic benefit at that point lay in a good thyroid history and evaluation not in fiddling with a radium bomb or elimination diets.

THE PHARYNX

Mucoproteinous edema of the pharynx initiates symptoms which though vague are persistent,[17] which, though unattended with objective inflammatory signs are pursued with therapeutic vigor ranging from local applications and antibiotics to tonsillectomy. The symptoms are chronic and long-standing and described variously as "sore throat," "throat discomfort," "lump in the throat," etc. True inflammation is absent. A suggestive pale and glossy edema of the pharyngeal mucosa is sometimes discernible. An inquisitive search will usually elicit a history of additional systemic symptoms of hypothyroidism. When the specific diagnostic tests are confirmatory the results with thyroid therapy are very pleasing.

REPORT OF A CASE

Mrs. C.R., a 34 year old white female, was seen in February, 1955. Her problem was recurrent sore throat and a feeling as though she had something in the hypopharynx which defied clearing. Her symptoms had been annoyingly present for years—sufficiently long so the exact time of onset was not clear in her mind. Though the winter season was the most aggravating period she felt that even in summer her throat was chronically troublesome. She had had tonsillectomy, repeated cycles of local treatment, and numerous antibiotic series. On several occasions she had been told there was nothing remarkable to be seen in her throat.

The patient's general history was not remarkable except for great fatiguability (she was often more tired in the morning than when she went to bed), cold intolerance, constipation and arthralgia. The latter was particularly troublesome in her hands. It took a period of use in the morning to get her fingers limber. She spoke of this problem as arthritis and felt it was in some way related to the "infection" in her throat.

This patient's examination was remarkable for the absence of inflammatory sign in her pharynx and upper respiratory tract. There was a suggestion of pale,

glossy edema of the pharyngeal mucosa—particularly of the posterior wall. It was not outstanding.

Her internist reported her general condition as satisfactory other than a mild secondary anemia. Her basal metabolic rate was reported as minus 28 per cent.

Dessicated thyroid grains one daily was given and three weeks later all of the patient's symptoms had improved greatly. After six additional weeks with grains one and a half daily she was free of throat symptoms, her arthralgia was gone, and she had normal vigor and sense of well being. She has had no problem with her throat since.

VASCULAR HEAD PAIN

The walls of the external carotid arterial tree are amongst the most active and symptomatic tissues in the head region. A wealth of clinical fact and hypothesis has accumulated around the subject of vascular head pain. No single formula for treatment has uniform success. Again the stumbling block is that of multiple etiology and the necessity in any case of an individual diagnosis. The factors of autonomic dysfunction and stress are well known. The close association with endocrine balance is evident in the cyclic history of some female sufferers. That the edematous substrate in the vessel wall of the hypothyroid sets the stage for some is less well appreciated. The classic myxedema heart undergoes this change to an extreme degree. Headache of vascular character and distribution is not uncommon as a presenting symptom in the hypothyroid patient.[19-22] It is relieved by adequate thyroid replacement. Reasonably enough it is not affected by the vast panorama of agents and techniques accumulated as easy single answers to this problem of multiple causation.

REPORT OF A CASE

Mr. R.T., a 27 year old white male, was seen in November, 1954. He had frequent head pains which he referred to as "sinus headaches." He had been troubled with them for several years. The aching was occipital as well as frontal. They were not cyclic in the manner of most vascular head pains. He had them almost every week. He also had moderate nasal congestion and postnasal drainage which clinched the diagnosis of sinusitis in his mind. The only seasonal variation of his headaches was increased severity in the cold weather. He felt worse generally in winter than in summer. He had no family background for his headaches. He seemed to be a well adjusted individual and professed no tension problems. Systemically he had no problems other than chronic fatigue. The latter had prompted him to have a general physical examination. No abnormalities were found.

The patient's ear, nose and throat examination revealed nothing remarkable. He certainly had no sinusitis. His nasal mucosal changes were those of a mild vasomotor rhinitis.

This patient's basal metabolic rate proved to be minus 29 per cent. He was given dessicated thyroid grains one and a half daily. When seen six weeks later he had had freedom from headache for almost three weeks—a quite remarkable achieve-

ment by his standards. Recheck two months thereafter confirmed the continuance of general well being and vigor and of freedom from head pain.

THE INNER EAR

Endolymphatic hypertension is descriptive of the inner ear phenomenon which became recognized a pathologic entity through the investigations of Hallpike and Cairns.[23] The gross dilatation of the endolymphatic system presented by them accounted for the advanced symptoms and clinical signs, both acoustic and vestibular, which have been termed variously Ménière's disease, endolymphatic hydrops, labyrinthosis, etc. Study of large groups of cases has demonstrated certain fundamental properties common to all. The disorder is first, (sometimes for many years or for its duration) a cochlear disturbance and secondly, vestibular. It is a disease of variable degree, from mild to destructive. It frequently remits spontaneously or by virtue of treatment. Its mild degrees are as reversible and advanced degrees as disastrous as those of vascular hypertension. Like vascular hypertension, every evidence suggests endolymphatic hypertension is a disorder of multiple etiology. Therefore it is apparent why no single approach to treatment has produced uniformly good results.

Endolymphatic hypertension requires first, an otologic diagnosis. The criteria are clear cut. Diagnosis in the early cochlear phase is a triumph and results in retained function. Aural pressure, broad spectrum tinnitus, distortion with impairment of discrimination beyond the degree of pure tone loss, the early flat or rising audiographic line, and recruitment are diagnostic. When the symptoms are minimal pressure, tinnitus and discrimination loss, tubal nonsense should be abhorred. The eager and repetitious catheter has been a poor substitute for diagnosis much over-long.

Advanced hearing impairment with a downsliding tracing, crippling distortion and frequently cyclic vertigo denotes the late stage of endolymphatic hypertension. Not too late, however, for a specific etiologic diagnosis. The old contention that this is a unilateral disease and not likely to affect the other ear is not true in the hypothyroid case. Bilateral involvement, early or eventual, is common.

The mechanism of endolymphatic fluid production and resorption remains an enigma. The typical clinical course of endolymphatic hypertension indicates that fault lies in excessive fluid production rather than faulty resorption. The dramatic suddenness of some attacks suggests a dynamic vascular or secretory influence. This is typified in the occasional but well documented ingestant allergic case. Clinical parallelisms with vascular autonomic dysfunction elsewhere in the body indicate that for some patients this is the basic mechanism

of the endolymphatic hypertensive disturbance.[24-26] Certainly for many patients endocrine imbalance plays a prominent role.[27] In the production of endolymphatic hypertension it frequently loads the gun that stress may pull the trigger. Hence for these patients the etiology is a composite of an endocrine background inadequacy and an immediate precipitating stress.

The relation of hypothyroidism to the inner ear is not a recent observation. Deafness is common in cretinism. In the early writings about myxedema VIII nerve neuritis was cited as a common occurrence. In many illustrative cases of myxedema in the literature hearing impairment was included in the long list of symptoms in the untreated patient. Interestingly enough among the improvements resulting from thyroid medication hearing gain was remarkable in some.[28,29] A summarization of knowledge of the thyroid gland, its function and disorders published more than ten years ago[30] drew attention to the relation of the ear to hypometabolism as follows:

"When deafness is associated with a lowered metabolic rate, either with or without the picture of myxedema, some improvement in audition frequently follows the administration of thyroid. This apparently holds true both in nerve and in middle ear deafness. For this reason it is recommended that the basal metabolism be determined in all cases of deafness.

"The vertigo of Ménière's syndrome may be alleviated greatly by thyroid administration, probably because of its dehydrating action."

These observations are penetrating. The empirical approach to "all cases of deafness" is unnecessary for the otologist. He can separate effusive otitis media and endolymphatic hypertension from the broad generalization of "deafness." To these former he can direct his thyroid investigation.

For the patient with endolymphatic hypertension who is found wanting in thyroid hormone one suspects that replacement therapy has more profound physiologic implications than simple "dehydration." In the minute anatomy of the stria vascularis and the nature of its supporting stroma, its vulnerability to mucoproteinous degeneration can be readily envisioned.[32] Alteration thereby in the control of endolymphatic fluid balance is a tempting hypothesis in the hypothyroid case. At any rate the hypothyroid endolymphatic hypertensive responds well to thyroid adequacy. The stresses of active life which previously precipitated endolymphatic crises are borne with labyrinthine equanimity.

REPORT OF A CASE

Mrs. J.D., a 26 year old white female, was seen on August 26, 1952. Ten days prior to examination she noted a plugged feeling in both ears when she awakened. There was no tinnitus, but sound was distorted. Six days later she experienced a mild vertiginous episode lasting ten minutes. Again on the morning of examination she had a similar attack. History evoked no other pertinent points.

The only physical findings of significance were those related to the inner ear. The patient exhibited recruitment, normal caloric response, inner ear type impairment with audiometric tracing as shown in Figure 1a.

Treatment with vasodilators and blocking agents intravenously and orally, salt restriction and diuretics for a period of three weeks was attended by improvement in the less involved ear to normal (Fig. 1b).

Though there were no suggestive signs of hypometabolism other than fatiguability, a basal metabolic rate showed minus 42 per cent with blood cholesterol of 248 mg per cent. One grain of thyroid was given each day for a week. At that time all imbalance and the sense of aural pressure were gone from the ear. The pure tone audiogram had not yet improved. Thyroid was increased to two grains daily. By December 20, 1952, all symptoms had subsided and hearing was normal (Fig. 1c).

Otosclerosis and endolymphatic hypertension sometimes coexist. Here an appreciation of the influence of the hypometabolic state on the inner ear is valuable preoperatively and postoperatively. It can alter the long term results of otosclerosis surgery.

REPORT OF CASES

Mrs. R.L., a 28 year old white female, was examined on February 9, 1953, because of hearing impairment. This had started in the right ear shortly after high school age and subsequently involved the left ear as well. There was a mild tinnitus in the right ear which did not annoy her particularly. She had never had vertigo. She was an adopted child and did not know her own family background. She was in good general health, and had not had physical examination in recent years.

Initial audiogram is seen in Figure 2a. Fork tests confirmed the bone conduction tracing. Her diagnosis was otosclerosis with cochlear defection of undetermined origin.

General examination demonstrated no abnormality other than mild secondary anemia. Basal metabolic rate was minus 24 per cent and blood cholesterol 167 mg per cent.

The patient was given two grains of thyroid per day and reexamined three weeks later. Subjectively she was delighted with her hearing improvement and it was borne out by testing (Fig. 2b).

On September 8, 1954, one and a half years later, her well-being and her cochlear reserve were both of a high order (Fig. 2c).

Mrs. C.D., a 34 year old white female, was examined January 16, 1950. She had bilateral hearing impairment which had been increasing since age 18 years. Her diagnosis was bilateral otosclerosis with a cochlear reserve adequate for fenestration. This was performed for the right ear on March 20, 1950. Her result was good as shown by her nine months postfenestration air conduction audiogram (Fig. 3a).

This level was maintained through the following years until the fall of 1955. On December 29, 1955, she gave the following history:

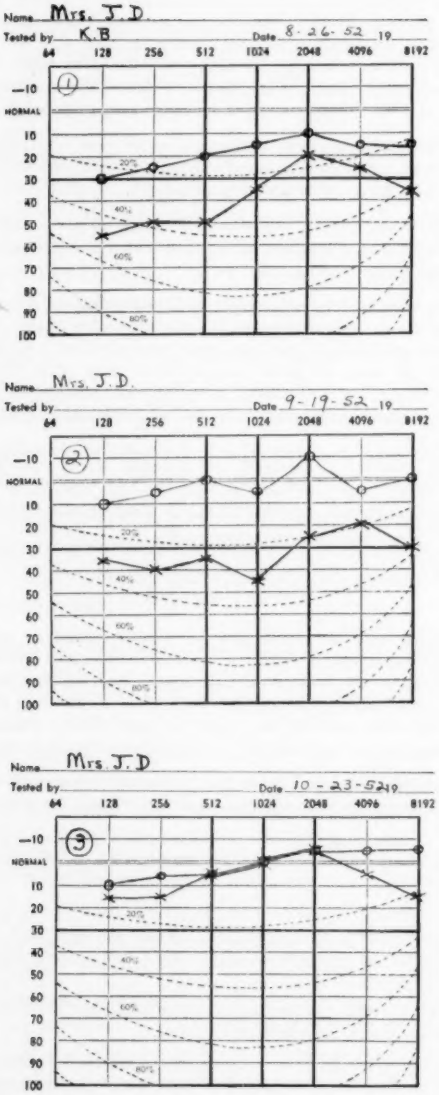

Fig. 1 (a).—Mrs. J.D. Pure tone hearing level at initial examination. Bone conduction and fork testing indicate the loss is purely inner ear. Recruitment is present in the left ear. Caloric responses are normal. Note moderate loss in right ear indicating bilateral involvement. (b) After three weeks of therapy with intravenous and oral vasodilators and blocking agents, salt restriction, and diuretics. Basal metabolic rate minus 42 per cent, blood cholesterol 248 mg per cent. (c) After three months of adequate thyroid replacement.

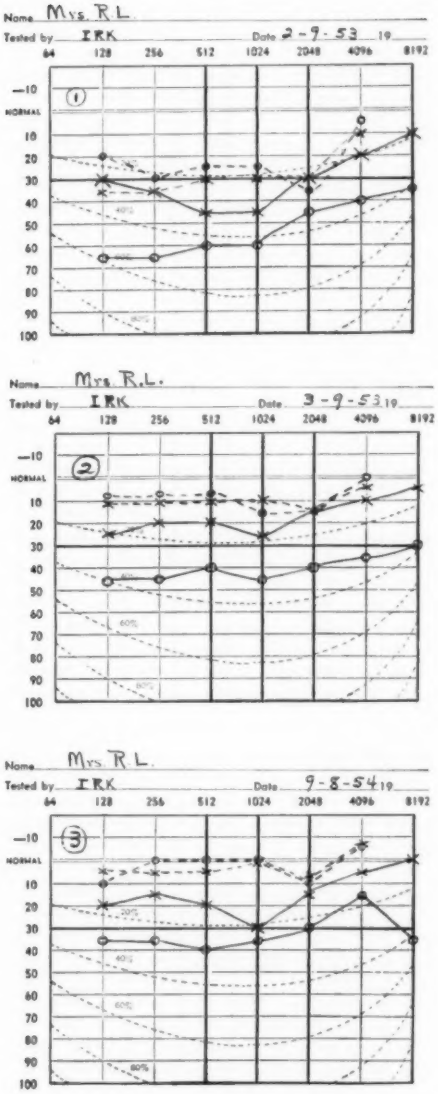

Fig. 2 (a).—Mrs. R.L. Initial audiogram. Cochlear defection confirmed with fork tests. Basal metabolic rate minus 24 per cent, blood cholesterol 167 mg per cent. (b) After two grains of dessicated thyroid daily for three weeks. (c) After one and one-half years of normal metabolic level.

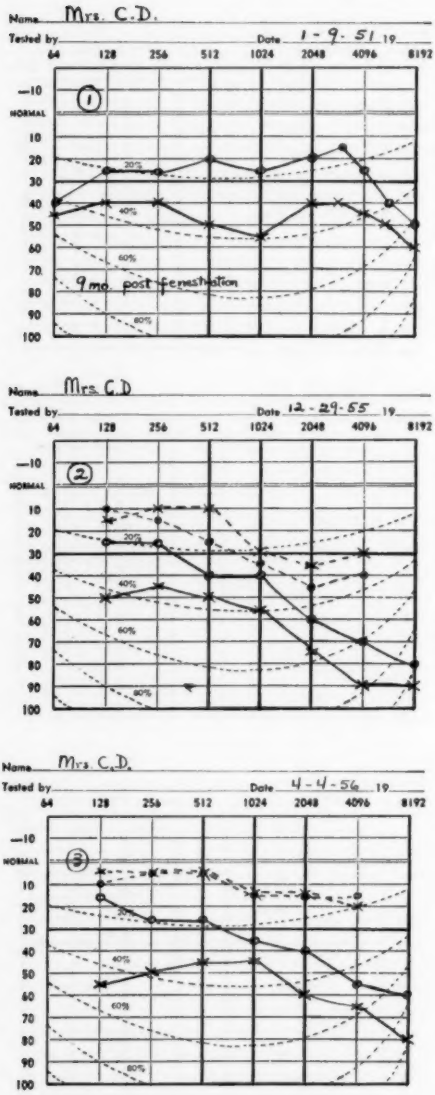

Fig. 3 (a).—Mrs. C.D. Post-fenestration (nine months) air conduction audiogram. (b) Two months after near-total thyroidectomy produced postoperative myxedema. Radioactive iodine uptake 6.5 per cent and low plasma hormone conversion rate. (c) Three months later with normal metabolic ba'ance restored with 0.8 milligrams thyroxin (Squibb) daily (2 grains of thyroid equivalent).

"In September because of a goitrous fullness of her neck she saw a general physician. He diagnosed multiple adenomatous goiter. In October, 1955, she had thyroidectomy. A month after her surgery she was disturbed by a sense of fullness and even pressure in both ears. There was also buzzing low and variable frequency tinnitus in both ears. Her hearing acuity decreased in both ears and she was sure her fenestrum was closing. Mild lightheadedness and giddiness, as she described it, became troublesome some mornings. First movements on arising or sharp changes of position during the day were prone to give a flash of dizziness requiring a moment's steadying. She had gained 10 to 20 pounds in weight in three months."

This patient had a completely altered physical appearance from her normal. She appeared much "older and puffier." Her skin was thick and dry. Her lower lids were pouchy. Her cerebration was slow but not too slow to be exceedingly depressed by her hearing loss (Fig. 3b).

Radioactive iodine uptake was 6.5 per cent with a low conversion rate to plasma hormone.

On January 9, 1956, she was given one-half grain of thyroid per day. Telephone report on January 30, 1956, noted freedom from giddiness and aural pressure and definite hearing gain. Replacement was increased to 0.8 milligrams of thyroxin daily (2 grains of thyroid equivalent). On April 4, 1956, all ear symptoms including tinnitus were gone and hearing for air and bone conduction sharply improved (Fig. 3c).

The old medical school adage that "treatment is easy once diagnosis is established" is never more true than in the problem of hypothyroidism. Replacement therapy with thyroid substance or, more accurately, with sodium levothyroxin itself is specific. The philosophy and dosage are available from authoritative sources.[1,11,31,33]

CONCLUSIONS

In otolaryngology hypometabolism is a clinical commonplace. The first requisite to its diagnosis is the knowledge that it is a daily visitor. The query, "How is your general health," is the most important single question in an otolaryngologic history.

Hypometabolism may be masked in the varied symptoms discussed.

The evaluation of the metabolic state is an important diagnostic effort. Precise methods are far superior to therapeutic guessing.

The results of specific therapy are a fine return for accurate diagnosis.

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XXXIV

FUNCTIONAL DISEASES OF THE NOSE

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One of the frequent omissions in our medical teaching today is a proper recognition and understanding of the functional diseases of the nose. When more physicians realize that perhaps 75 per cent of all nasal complaints coming to a doctor's attention are functional rather than organic in nature, then there will be fewer ineffectual nasal and paranasal operations, there will be fewer disappointments from the indiscriminate use of vaccines, vitamins and antibiotics and there will be fewer useless trips to Arizona. I make this statement objectively and impersonally for I continue to perform my share of nasal and paranasal surgical procedures, but I reserve such measures for organic nasal pathology.

When I began a study of this subject in 1931, there were too many ear, nose and throat patients suffering from operative atrophic rhinitis. There were too many people who needed a change in their habits of living, or a study of their endocrine system, or an investigation of their body chemistry, or some other medical explorement rather than the removal of organically normal but physiologically malfunctioning nasal mucous membranes.

In order to understand the functional diseases of the nose, one must comprehend these affections in terms of their inclusions and exclusions.

To be specific I offer the following definitions and explanations as a guide to our study.

DEFINITIONS AND EXPLANATIONS

a) A *functional disease* of the nose is a condition of abnormal physiological response in which the mucous membrane of an organically normal nose enters into a state of hypo- or hyperactivity.

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I concede the difficulity of shaping a definition to conform to such a flexible term as "organically normal," but in this regard I appeal to your liberal interpretation.

In the functional diseases of the nose some agent external to the olfactory organ (but not necessarily external to the body) causes the nasal mucosa to underwork or to overwork, and such a response is always temporary and reversible in character. When the causative agent in an uncomplicated functional disease of the nose is removed, the symptoms it has caused disappear and the patient is well.

EXAMPLES OF FUNCTIONAL DISEASES OF THE NOSE:

1. *Hypofunction.* Atropine produces a temporary and reversible hypoactivity of the nasal mucosa.

2. *Hyperfunction.* Mildly irritating inhalants produce a temporary and reversible hyperactivity of the nasal mucosa.

b) An *organic disease* of the nose is a condition of structural change in which the nose presents evidence of destruction or proliferation of tissue or in which it manifests anatomic deformity resulting from developmental or traumatic causes.

May I repeat that everything I say concerning the functional diseases of the nose applies only to those olfactory and respiratory segments that are organically normal. The moment a hypo- or hyperfunctioning nasal mucosa develops destructive or proliferating changes that nose is automatically excluded from the classification of a functional disease of the nose.

The therapeutic approach to a functional disease is one thing; the therapeutic approach to an organic disease is another thing.

Organic disease produces a change in structure; functional disease produces a change in physiological response.

EXAMPLES OF ORGANIC LESIONS OF THE NOSE:

1. *Destructive Lesions.* Lues and tuberculosis are destructive agents that can produce nasal erosions.

2. *Proliferating Lesions.* Chronic sinusitis and malignancies are proliferating agents that can produce polypi or tumors.

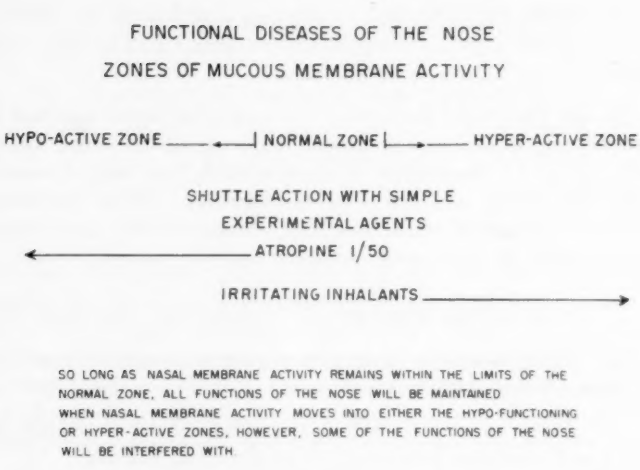
FUNCTIONAL DISEASES OF THE NOSE
ZONES OF MUCOUS MEMBRANE ACTIVITY
HYPO-ACTIVE ZONE
NORMAL ZONE
HYPER-ACTIVE ZONE
SHUTTLE ACTION WITH SIMPLE
EXPERIMENTAL AGENTS
ATROPINE 1/50
IRRITATING INHALANTS
SO LONG AS NASAL MEMBRANE ACTIVITY REMAINS WITHIN THE LIMITS OF THE NORMAL ZONE, ALL FUNCTIONS OF THE NOSE WILL BE MAINTAINED WHEN NASAL MEMBRANE ACTIVITY MOVES INTO EITHER THE HYPO-FUNCTIONING OR HYPER-ACTIVE ZONES, HOWEVER, SOME OF THE FUNCTIONS OF THE NOSE WILL BE INTERFERED WITH

Fig. 1

In organic nasal diseases the so-called therapeutic response is said to be irreversible not because a luetic or tuberculous lesion cannot heal, but because it rarely heals without some fibrotic change.

c) A mucous membrane is an epithelial tissue, one purpose of which is to produce mucus.

So far as the nasal mucosa is concerned, however, it must produce just so much mucus. It if produces any less or any more than a certain amount, there develops a state of hypo- or hyperactivity in which some of the functions of the nose will be interfered with—and such interferences will produce symptoms for which the doctor will be consulted.

Perhaps we should be more technical and make plain that the amount of mucus produced is simply an index of the mucosa's physiological activity which may be normal, less than normal, or greater than normal.

May I continue to stress the importance of the nose producing just the proper amount of mucus if its functions are to be maintained.

The whole question of nasal mucosa activity presupposes 1) that the mucous membrane under consideration is a normal functioning

epithelium which misbehaves only because some agent external to the nose makes it misbehave; 2) that when such an external agent becomes effective, the amount of mucus secreted decreases or increases in either a hypofunctioning or hyperfunctioning manner.

Shall we express this situation diagrammatically?

In Figure 1 we describe a line. On this line we plot a central or normal zone. To the left we lay out the hypoactive zone; to the right the hyperactive zone.

According to our thesis, if the nose in question exhibits no organic pathology and for no other reasons excludes itself from the classification of functional diseases of the nose, we assume so long as the amount of nasal mucus produced keeps within the confines of the normal zone, that the functions of the nose will be maintained. If, however, the amount of mucus decreases enough to cause this shuttle index of mucosal activity to move to the left and into the hypoactive zone, or if it increases enough to cause this shuttle index to move to the right and into the hyperactive zone, then some of the functions of the nose will be interfered with.

Prosaic as this experiment may be, we present it in all of its selv-evident nature. The purpose of the experiment is to cause an organically normal nasal mucosa a) to hypofunction and b) to hyperfunction.

Hypofunction. 10 adults given 1/50 of a grain of atropine sulphate hypodermaticlly developed dry noses within a period of 30 minutes.

By this test the shuttle index moved to the left and into the hypofunctioning zone.

Hyperfunction. Ten adults exposed to onion emanations developed a runny stuffy nose within five minutes.

The reversibility of these reactions was noted in the return of the shuttle index to the normal zone after the following intervals: a) the hypofunctioning noses returned to normal in 12 to 14 hours; b) the hyperfunctioning noses returned to normal in 30 to 60 minutes.

COMMON FUNCTIONS OF THE NOSE

Figure 2 is Figure 1 to which has been added some of the common functions of the nose.

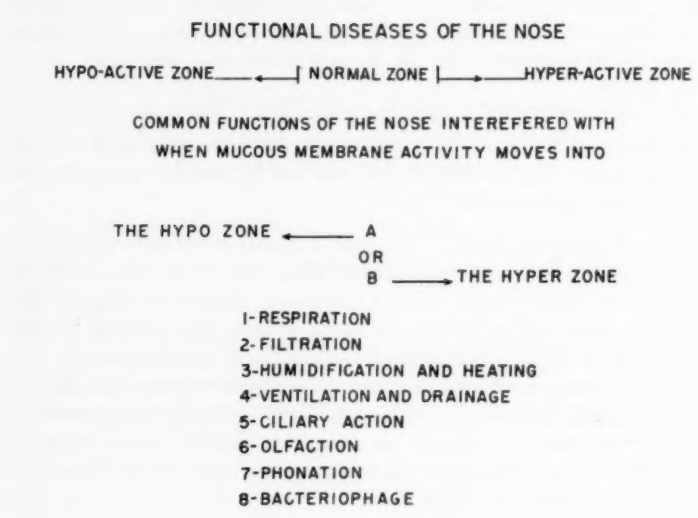

Fig. 2

We have spoken of the shuttle index of mucosal activity and have hinted that whenever this shuttle passes out of the normal zone, some of the functions of the nose are interfered with.

What then are the functions of the nose that can be interfered with when a normal nasal mucosa enters into a state of hypo- or hyperfunctional activity?

Briefly, the common ones are as follows:

1. *Respiration.* The nose is the peripheral organ of the respiratory system. We grant that a person can live without breathing through his nose but he cannot do so without certain unsalutary results.

2. *Filtration.* The vibrissae (or hairs within the nostrils) act as an inefficient sieve to separate gross particles of foreign material from the inhaled air. Ciliary action, however, has to take care of the foreign substances that pass through the vibrissae.

3. *Humidification and Heating.* A proper amount of mucus in the nose is the means by which inhaled air takes on heat and moisture that is carried throughout the respiratory tract.

4. *Ventilation and Drainage.* The physical and physiological importance of nasal ventilation and drainage is an incompletely explained phenomenon.

One thing, however, is evident, namely that interference with these functions produces some of the more serious nasal complaints.

5. *Ciliary Action.* The cilia act as brooms by which the nose sweeps mucus and foreign material out of the nasal cavity. This process is a procedure which is supplemented by the filtration action of the vibrissae and the physical drainage of the nose.

6. *Olfaction.* The sense of smell depends for its sensory reception, in part at least, on an unobstructed path to its end organ in the superior meatus and to a normal condition of the mucosa which contains it.

7. *Phonation.* The nasal tone accompanying a cold or hay fever is adequate evidence of the importance of the nose as a resonance box for speech.

8. *Bacteriophage.* So far as I know the bacteriophage properties of the nose are inadequately comprehended. Nasal mucus may or may not have antibiotic properties.

THE HYPOTHESIS CONCERNING FUNCTIONAL DISEASES OF THE NOSE:

1. All things being equal so long as a nose that is without "organic pathology" continues to secrete a normal amount of mucus, all the functions of the nose will be maintained.

2. If, however, an exciting agent (external to the nose but not necessarily external to the body) causes a hypo- or hyperactivity of the nasal mucosa, then some of the functions of the nose will be interfered with.

3. This interference of nasal function will result in signs and symptoms characteristic of either a hypo- or hyperfunctioning rhinitis.

4. Hypo- or hyperfunctional diseases of the nose are mucous membrane responses that are temporary in nature and reversible in

reaction. Elimination of the cause automatically relieves the abnormal response.

5. If such physiological diseases develop organic pathology they can no longer be classified in our concept of the functional diseases of the nose.

INDUCTIVE APPROACH TO THE STUDY

In observing various types of hypo- and hyperfunctioning diseases of the nose, we shall not analyze the agents causing alterations in mucosal activity, neither shall we investigate the mechanisms by which physical, physiological or psychological stimuli produce an alteration of function, but we shall approach this study in an inductive manner and endeavor to correlate a particular syndrome with its nasal response.

EXPLANATORY NOTES

1. One should recognize that both the hypofunctional and hyperfunctional diseases may manifest themselves in one of two phases: either a) the transitory form which is reversible in a period of hours; or b) the prolonged form which is reversible in a period of months.

2. Failure to demonstrate reversibility within a reasonable length of time suggests the development of organic changes the result of overstimulation or overexposure.

3. The terms "acute" and "chronic" are avoided because they may connote tissue changes which would exclude them from the functional disease classification.

HYPOFUNCTIONING DISEASES OF THE NOSE

Figure 3 is Figure 2 to which has been added an incomplete list of nasal syndromes exemplifying hypofunctioning rhinitis.

Sample types of hypofunctioning rhinitis, as identified by their causative agents, are:

1—Atropine
2—Physical
3—Psychic
4—Febrile
5—Debilitating (or constitutional)

(There are many others)

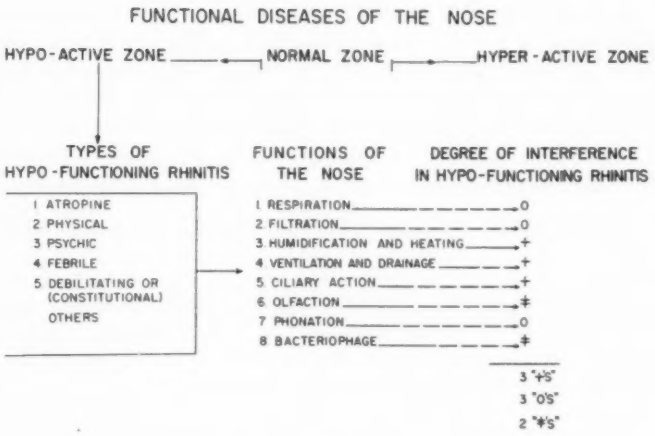

Fig. 3

Collectively, and as shown in Figure 3, the group of hypofunctional diseases has been matched against the functions of the nose and the degree of interference noted. In Figure 3, atropine is the exciting agent against which the selection and degree of interference with nasal function is measured.

Individually we shall discuss each type of hypofunctioning disease in terms of its clinical manifestations and interpretations.

DEFINITION

A hypofunctional disease of the nose is a condition in which an exciting agent external to the nose (but not necessarily external to the body) causes an otherwise normally performing mucous membrane to *decrease* its production and thereby to produce a temporary and reversible interference with some of the nasal functions.

Symptoms of Hypofunctioning Diseases of the Nose: 1) A feeling of dryness in the nose and throat; 2) often a thick, scanty or scabby nasal or postnasal discharge which may be diagnosed as a sinusitis (usually a sphenoidal infection); 3) occasionally there is a sense of inadequate breathing space, a symptom commonly observed in an organic atrophic rhinitis.

DIFFERENTIAL DIAGNOSIS

Because both a hypofunctioning rhinitis which is a physiological response and an atrophic rhinitis which is an organic change, have in their early stages the same signs and symptoms, one may have to delay the ultimate differentiation between these two conditions until the reversibility of the functional affection becomes evident.

DISCUSSION OF TYPES OF HYPOFUNCTIONING RHINITIS

1. *Atropine Rhinitis (Hypofunctioning)* (previously described).

Transitory Form. The property of atropine sulphate to arrest the production of bodily secretions is a well-known physiological reaction. Its use as a preoperative medication is contingent upon its ability to induce a hypofunctioning rhinitis.

Prolonged Form. Continued use of belladonna, phenobarbital and atropine or atropine eye drops is responsible for this type of nasal dysfunction.

2. *Physical Rhinitis (Hypofunctioning).*

Transitory Form. The transitory form of physical rhinitis is a rhinitis sicca brought about by sporadic exposure of the nasal passages to an atmosphere sufficiently dry and warm to cause evaporation of nasal moisture, but not sufficiently so to produce an edematous reaction.

This condition can occur in any of us, but furnace men, dry cleaners, evaporator workers and others similarly employed, whose periods of exposure to such an atmosphere is mild in degree and short in duration, exemplify this form of nasal difficulty.

Prolonged Form. A prolonged physical hypofunctioning rhinitis is observed in patients living or working in warm rooms that are inadequately humidified and in persons whose nasal mucosa is laid open to mildly desiccating fumes.

This condition too can occur in any of us. Occupational examples of this type of nasal dysfunction are seen in kiln operators, foundry workers, and bake oven mechanics. Seldom does this condition result in structural damage.

3. *Psychic Rhinitis (Hypofunctioning).*

Transitory Form. Everyone is subject to a transitory psychic hypofunctioning rhinitis. How often a dry mouth (and nose) precedes a speech or an appearance before the microphone. This exasperating circumstance is a psychic hypofunctioning response. The pitcher of water is on the banquet table not because the speaker is thirsty. He is not thirsty; he is dry!

All too frequently little anxieties (many of which are almost unrecognized) express themselves in a dryness of the mouth and nose.

Prolonged Form. As a fleeting anxiety produces a transitory psychic hypofunctioning rhinitis, so enduring anxiety produces a prolonged response.

Our mental hospitals are filled with patients who long before their commitments had an annoying psychic hypofunctioning rhinitis, the significance of which was unrecognized and the treatment of which was empirical or sinus-wise.

4. *Febrile Rhinitis (Hypofunctioning).*

Transitory Form. Repeatedly I have been called upon to treat a posterior "sinus infection" in a pneumonia patient—one who has maintained a temperature of 105° for several days—only to discover that following the crisis the "sinusitis' disappeared with remarkable rapidity.

Frankly, a febrile rhinitis does present the signs and symptoms of a subacute sphenoidal sinusitis, but experience teaches one to wait for the diagnosis to establish itself.

Prolonged Form. So long as a fever lasts, the febrile hypofunctioning rhinitis may continue. In the days of typhoid fever, malaria, smallpox, and other forms of extended febrile states, the prolonged form of febrile rhinitis was common—today it is not so frequent.

5. *Debilitating or Constitutional (Hypofunctioning).*

There is no *transitory form.*

Prolonged Form. Although the sedentary life of a chronic invalid predisposes him to a dry and scabby nose, even a short period of

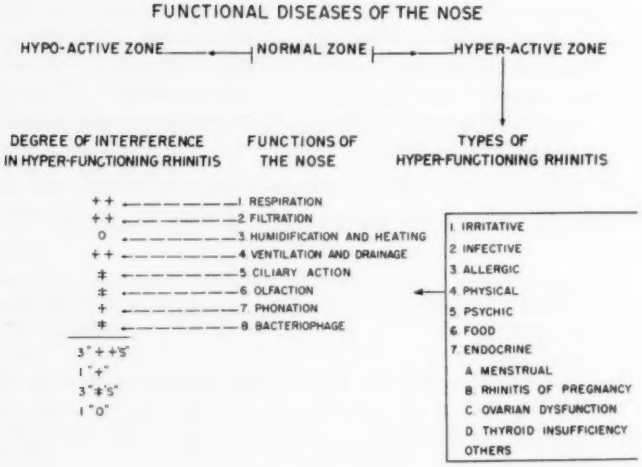

Fig. 4

general improvement can bring about a betterment of the nasal condition.

HYPERFUNCTIONING DISEASES OF THE NOSE

Figure 4 is figure 3 in which some of the types of hyperfunctioning rhinitis are substituted in place of some of the types of hypofunctioning rhinitis.

Sample types of hyperfunctioning rhinitis as identified by their causative agents are:

1—Irritative

2—Infective (Common Cold)

3—Allergic

4—Physical

5—Psychic

6—Food

7—Endocrine

A. Menstrual
B. Rhinitis of Pregnancy
C. Ovarian Dysfunctions
D. Thyroid Insufficiency

(There are many others)

Collectively as shown in Figure 4 (and as patterned under the hypofunctioning classification), the hyperfunctioning diseases have been matched against the common functions of the nose and the degree of interference noted.

In Figure 4 irritative rhinitis is the exciting agent against which the selection and degree of interference with nasal function is measured.

Each of the following causative agents has its own characteristic reactions. Individually (also as patterned in the presentation of the hypofunctioning diseases of the nose), we shall discuss each type in terms of its clinical manifestations and interpretations.

A hyperfunctional disease of the nose is a condition in which some exciting agent external to the nose (but not necessarily external to the body) causes an otherwise normally performing mucous membrane to *increase* its usual activity and thereby produce a temporary and reversible interference with some of the functions of the nose.

Symptoms of hyperfunctioning diseases of the nose are: 1) nasal obstruction, 2) rhinorrhea, 3) intranasal pressure, 4) headaches, 5) postnasal discharge (all the signs and symptoms of a common cold or sinus infection).

By way of warning may I counsel the reader against any oversight or indifference in regard to the hyperfunctioning diseases of the nose. The hyperactive nose is one that exhibits signs and symptoms that are so familiar to us, those of the common cold, those of its complicating sinusitis, or those of an allergic rhinitis.

Too many practitioners continue to regard a "runny nose" as a cold, as a sinusitis, or as an allergy, and well they may be the causes too, but failures in the treatment of these ailments have an explanation which is ofen an unrecognized or unsuspected hyperfunctioning rhinitis, the causative agent of which is evident only after investigation and study.

Intranasal surgery to relieve an uncomplicated hyperfunctioning rhinitis may be unwise and ineffective; intranasal surgery to relieve an organic diseases may be discerning and efficacious.

DISCUSSION OF TYPES OF HYPERFUNCTIONING RHINITIS

1. *Irritative Rhinitis (Hyperfunctioning).*

Transitory Form. Previously we have mentioned the production of a hyperfunctioning rhinitis by the inhalation of onion emanations.

The diagnosis of a transitory irritative hyperfunctioning rhinitis is self evident. The patient has been exposed to irritating inhalants or instillations and he knows it. Only when the concentration of the stimulating agent is great or the length of the exposure protracted, need one suspect an organic complication.

Prolonged Form. The present age is one of noxious fumes, of penetrating dust, of smoke filled rooms, of nonallergic face powders and cosmetics, and of all sorts of nasal instillations. Frankly the prolonged form of irritative rhinitis is common but often unsuspected or unrecognized.

All of us are victims of an irritating rhinitis to some degree. Garage workers, furniture makers, musicians, welders and building painters are but a few of the types of laborers subjected to this sort of malady.

From my experience I am convinced that one of the most common causes of a prolonged irritative rhinitis is the persistent use of nose drops. Any nose drops used long enough will produce the very symptoms they are taken to relieve.

2. *Infective Rhinitis (Hyperfunctioning).* (The common cold). The common cold is a hyperfunctioning rhinitis, the exciting cause of which is a respiratory infective agent or virus. It may or may not be initiated by exposure to cold or dampness.

An uncomplicated cold lasts for 21 days. If someone tells you otherwise, do not believe it.

The course of an infective rhinitis is divided into three stages which follow a rather exact time table. Diagrammatically, we represent this occurrence in Figure 5.

COMMON COLD (UNCOMPLICATED)
STAGES AND TIME—TABLE

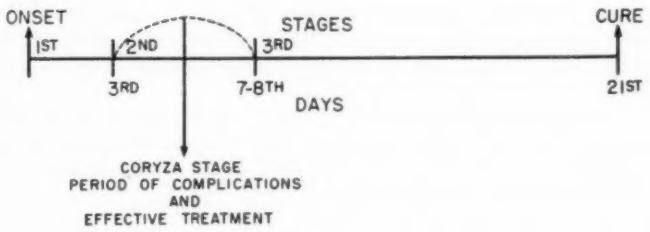

Fig. 5

The first stage of the common cold continues for 48 hours and may or may not be noticed by the patient. Its symptoms, if present, are a slight throat irritation or cough.

An uncomplicated second stage begins on the third day and remains through the seventh or eighth day. Its symptoms are those of a coryza or cold. It is in this stage that the shuttle index of mucosal activity extends far into the hyperfunctioning zone; it is in this stage that so many of the functions of the nose are interfered with; it is in this stage that the symptoms are most severe; it is in this stage that complications occur (most of which are due to an impedance of the function of ventilation and drainage). At some time around the seventh or eighth day following the onset of an uncomplicated cold, the nose opens spontaneously and thereby restores its function of ventilation and drainage. With the attainment of this goal, all functions of the nose return and the cold passes into the final period.

In the third stage of an infective rhinitis the nose is open and draining a mucopurulent material which gradually becomes normal in amount and character. During this time the patient uses three handkerchiefs a day; two handkerchiefs a day, and then one handkerchief a day. Because the cessation of the second stage brings with it a return of nasal functions, the patient insists that at the end of the

second stage the cold is over. The fact that a mucopurulent discharge continues up to the twenty-first day does not interest him for the shuttle index of mucosal activity has returned to the normal zone and so far as he is concerned the nose is well.

From this observation of the stages and the time table of an infective rhinitis, nature appears to teach us that the way to cure a common cold is to establish ventilation and drainage. In my opinion, only those measures that bring about ventilation and drainage have any value in the treatment of an infective hyperfunctioning rhinitis—and this statement applies both to local and systemic therapeutic measures.

The management of the common cold, in accordance with its stages and time table, is a must for every practitioner of medicine, for only by understanding a cold's habits and vagaries can one outwit this commonest of man's afflictions.

The subject of outwitting the common cold, however, is a treatise in itself.

3. *Allergic Rhinitis (Hyperfunctioning).* I do not intend to dissertate on an alergic rhinitis but I do wish to emphasize two points, namely: a) that an uncomplication allergic rhinitis is a hyperfunctioning disease of the nose. Only when the allergy becomes complicated by polypi or hyperplasias does it take on an organic character, and b) an allergic nasal mucosa is pale; all other hyperfunctioning mucosae are red. The swelling of an allergic mucous membrane is caused by distention of intercapillary spaces which contain few red blood cells, consequently the pale color. The swelling of all other hyperfunctioning mucous membranes is caused by a distention of the capillaries themselves, which contain an abundance of red blood cells, consequently the red color.

This point of differentiation is a study that we still have under investigation.

4. *Physical Rhinitis (Hyperfunctioning).*

Transitory Form. This type of nasal dysfunction occurs in the patient who says that he is all right so long as he remains indoors but when he goes out-of-doors, he develops a cold. It also appears in the patient who says that he is all right so long as he remains out-of-doors,

but when he goes into a heated room he develops a stuffy nose. I do not know the answer to this problem.

Prolonged Form. Air conditioning, jobs in and out of cold storage vaults, continuous employment in cold or freezing temperatures are only a few of the purported causes of a physical hyperfunctioning rhinitis.

5. *Psychic Rhinitis (Hyperfunctioning).* (See psychic hypofunctioning rhinitis.)

Transitory Form. Previously we have noted how anxieties can produce a dry nose and throat. In the same manner, but not always from the same causes, they can produce a rhinorrhea. Exampls: 1) For years I had under observation a minister who had a "runny, stuffy nose" that lasted two hours preceding each Sunday sermon. With the onset of his discourse the cold disappeared for another week. 2) I have had several patients who in fits of anger developed a profuse rhinorrhea that continued as long as the emotional disturbance lasted.

Prolonged Form. Example: A southern girl married a northern boy and the couple settled in New York State. For more than a year following their marriage the wife had a continuous cold which responded to no treatment. For this difficulty she consulted many doctors. I saw her twice and referred her to a neuropsychiatrist who discovered that the cause of her hyperfunctioning rhinitis was not any condition associated with her marriage, nor was it the result of the inclement weather of the North, but was a drunken father-in-law. In a home of her own she became well.

6. *Food (Hyperfunctioning).* Long have I contended that certain types of food rhinitis are quite independent of and unrelated to an allergy. Such food responses present no lacrymations, not itching of eyes or palate, and no pallor of the mucous membrane or other signs and symptoms characteristic of an allergic rhinitis.

To date I have not been able to isolate nor to identify defendable cases of transitory nonallergic food rhinitis.

Prolonged Form. So far as the prolonged type of nonallergic food rhinitis is concerned, however, I consider it a physiological entity. Example: A girl nine years old suffered from a continuous "cold" and sinusitis for six years. During this time she underwent

the following precodures: 1) two tonsillectomies and adenoidectomies, 2) nasal suction treatments twice a week for six years, 3) a subsequent adenoidectomy, 4) an antrum window operation, 5) several other unidentified operative procedures. When a third adenoidectomy was advised, she came to my attention. Objectively this girl presented the signs and symptoms of a chronic pansinusitis. A study of her history revealed that for years she had eaten candy to excess and to the exclusion of other important nutrients. Elimination of the candy from her diet brought about a complete cessation of her symptoms—all of which disappeared within two weeks of the time I first examined her. I saw this child just twice. Twenty years have now passed since she had her food rhinitis and she continues to remain well except when she goes on a candy binge.

Briefly, potatoes, starches, citrus fruits, or an inadequate intake of proteins and vegetables are the common causes of a food rhinitis.

7. *Endocrine Rhinitis (Hyperfunctioning):* a) menstrual, b) rhinitis of pregnancy, c) ovarian dysfunction, d) thyroid insufficiency.

Endocrine rhinitis does not manifest itself in a transitory form.

a) *Menstrual Rhinitis.* The signs and symptoms of a menstrual rhinitis resemble those of a common cold. It comes on three to four days prior to the menstrual period and disappears soon after its onset. It is not of common occurrence. It has been observed by me only during the first year of menstruation.

It is not prevented or controlled by vaccines, antibiotics, vitamins, or other therapeutic measures usually employed in the treatment of the common cold, but it can be, and often is, corrected by esterogenous substances.

Unfortunately, an endocrine extract that cures one patient may be ineffective with another.

b) *Rhinitis of Pregnancy.* The rhinitis of pregnancy is a hyperfunctioning disease of the nose that is common. It may appear at any time during gestation and it rarely, if ever, disappears until the termination of the pregnancy or shortly thereafter. It does not give the appearance of an allergy. The signs and symptoms are those of a severe infective rhinitis but the response to measures ordinarily used in the treatment of the common cold are of little or no benefit.

Thyroid extract, antihistaminics, antibiotics and even the esterogenous substances that I have used have not relieved this condition. Local vasoconstriction, of course, produces temporary ventilation and drainage.

The subject of rhinitis of pregnancy warrants thorough scientific investigation.

c) *Ovarian Dysfunction.* I have observed many patients in whom there have been associated the signs and symptoms of an ovarian disease and those of a hyperfunctioning rhinitis. In many instances I have seen the correction of the ovarian difficulty bring about a complete relief of the nasal dysfunction. Example: A woman, aged 38, had complained of a stuffy nose since the onset of menstruation at the age of 13. At age 37, she developed a demonstrable ovarian disease which required a bilateral oophorectomy. Following this operation all nasal symptoms disappeared. When, however, her internist prescribed ovarian extract for the essential requirements of her body the rhinitis returned.

d) *Thyroid Rhinitis.* Any patient the cause of whose hyperfunctioning rhinitis has not been determined by proper differential diagnosis should be given provocative doses of thyroid extract. Some hyperactive noses clear completely with thyroid therapy, and this statement holds regardless of the presence of a normal basal metabolic rate and regardless of the concurrence of a complicating sinusitis.

I do not know the explanation of this situation.

We have given no consideration to many other types of hyperfunctioning rhinitis, in particular I mention the dysfunctions due to alcoholism and sexual excitation.

COMMENTS AND CONCLUSIONS

1) Years of experience and observation have convinced me that too many doctors are treating noses according to the old adage that every "runny nose" is the result of a cold, an allergy or a sinusitis.

The acceptance of this doctrine leaves many types of hyperfunctioning rhinitis inadequately treated and unimproved.

2) A sinusitis complicating a hypo- or hyperfunctioning rhinitis often receives the attention that the underlying functional disease of the nose should get.

3) Operative procedures for the relief of symptoms of hypo- or hyperfunctioning diseases of the nose in the absence of organic pathology are usually of little value.

4) Operations for the relief of organic diseases of the nose may be of great value.

5) This study of the functional diseases of the nose is not a crusade to reduce the amount of nasal and paranasal surgery; it is merely a remedial enterprise the purposes of which are: a) to recognize the presence, the frequency and the importance of the functional diseases of the nose; b) to discover an underlying functional disease even though it simulates a more common nasal affection with or without a complicating sinusitis; c) to institute the treatment such a dysfunction properly requires.

277 Alexander St.

XXXV

UNUSUAL VIRUS DISEASES IN OTOLARYNGOLOGY

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The subject of virus diseases is one with which we in our specialty must be thoroughly familiar. The full gamut of transition from the age of focal infection to antibiotic control of diseases has occurred during our short association with otolaryngology. We are now faced daily, in our clinics and offices, with the patient showing unusual and persistent symptoms which do not respond to the older orthodox procedures or to the most recent broad spectrum antibiotics, even with their exaggerated economic costs to the patient. We must consider whether the virus diseases are about to take over our practices, either because we have not satisfactory defense against them, or that they have become increasingly strong with our apparent conquering attack on the bacterial world. With this in mind I would like to enlist interest in the consideration of a few of the more unusual virus infections that might be of special concern to the otolaryngologist.

The word virus means poison, but it was first applied to any toxic substance that could pass through an earthenware filter which would trap true microbic organisms. Size, therefore, is a primary characteristic, and at first this material was invisible, but with the development of the electron microscope, the shape and size of various strains could be recognized. The next most important characteristic of viruses is that they manifest themselves and multiply only in susceptible living cells. The method of invasion and combination with individual cells is still largely unknown. The importance of this is that living tissue is necessary in any virus study, and one must use either living animals or a live tissue culture for their study. The development of animal inoculation, chick embryo, or tissue cultures either in embryonal

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human tissue or the "HeLa" cells of a known cancer stain, have all been used in the study of these diseases.

CLASSIFICATION OF VIRUS DISEASES

There is no satisfactory or accepted classification of the virus diseases. Due to so many subgroups in the various broad clinical pictures one only gets more confused by their study. A rough clinical classification seems more to the point and one is presented below.

CLINICAL CLASSIFICATION OF VIRUS DISEASES

THE POX AND RASHES	Small pox earliest recognized and controlled
LIVER VIRUS DISEASES	a) Infections } Hepatitis, Yellow Fever b) Serum }
RESPIRATORY TRACT	a) Influenza } Can be proven by Lab. test b) A.R.D. } c) Common Cold—Hodge-podge of many viruses, cannot be grown—know little about it
ENCEPHALITIS AND MENINGITIS	a) Disease of animals—men secondary b) Mosquitoes transfer to men c) Have occurred in epidemics
POLIOMYELITIS & ITS COUSINS	a) Polio—3 main types—1, 2, 3 b) Coxsackie—*Group A*—Herpes, muscle pain *Group B*—Bornholm Disease c) E. M. C.—Encephalomyocarditis
INFECTIONS OF SKIN AND BRAIN	a) Herpes Simplex b) Herpes Zoster c) Chicken Pox d) German Measles e) Measles

Rabies existed 4000 years ago. Pasteur's crowning work.

It would take several tables to show the subclassification of acute respiratory diseases above. These are known in England as the acute febrile catarrh group. It is unfortunate that the large group of the common cold still remains as elusive as before.

THE ADENOIDAL PHARYNGEAL CONJUNCTIVAL VIRUSES

In the respiratory tract group has been found a relatively new division known as the adenoidal-pharyngeal-conjunctival or A.P.C. viruses. This group has been described by Bell[1] and his co-workers as "viruses of the respiratory tract, nonpathogenic for laboratory animals, ether resistant, heat labile, filtrable, and resistant to antibiotics." There is a group reaction by complement fixation which is not specific as to individual types. There are, however, eight distinct immunological types. Five of these types (1, 2, 4, 5, 6) have been cultured from adenoid and tonsil tissue. Type 3 has been repeatedly cultured from the throats and conjunctiva of the definite disease entity called acute pharyngeal-conjunctival fever.

Acute pharyngeal-conjunctival fever is a mildly epidemic type of disease that has been reported from Washington,[1] San Francisco[2] and Toronto.[3]

In Toronto twenty adults were referred to the laboratory of Dr. Hugh Ormsby, of the Department of Ophthalmology in the six months following November 1951 with conjunctivitis and other symptoms of the disease. Of these, seven produced a virus which grew in tissue cultures of monkey-kidney epithelium or "Hela" cells. Type 3 A.P.C. group was proven to be present. It is of interest that in adults the clinical symptoms seemed first to be a follicular conjunctivitis in one eye. Followed in three to four days by involvement of the other. Pharyngitis occurred only in two of the patients and catarrhal otitis in one. None had fever, malaise or muscle pains.

The disease in children was more thoroughly studied during a local epidemic, beginning in early August 1955, by Dr. Ormsby and his group. The clinical course was much more like the reported findings in other centers and closely followed the Washington report. Many had a temperature elevation to 102° to 105° F., acute pharyngitis was present, and catarrhal otitis media was a common complication. As the disease was apparently associated with swimming pools, a survey was made within a half mile of a North Toronto pool. It was found that half of the cases had occurred in that area. Seventy-four gave a history of swimming in that pool within ten days of the onset of the disease, six had been in pools elsewhere.

The one significant point is that while most of the work on this disease entity has been largely the interest of the ophthalmol-

TABLE I.

Cases of A. P. C. Fever Occurring Within a Half Mile Radius of a North Toronto Indoor Swimming Pool (August, 1955)

(Ormsby and Aitchison)

Cases originating in pool (all children)	74
Cases originating in pools elsewhere	6
Cases originating from direct contact at home	31
No history of swiming or contact at home	1
TOTAL CASES	112

TABLE II.

Symptoms of Pharyngeal-Conjunctival Fever in 112 Patients (August, 1955)

(Ormsby and Aitchison)

	CHILDREN (104)	ADULTS (8)
Sore Eyes	68	7
Fever, Malaise and Muscle Pains	75	2
Sore Throat	63	1
Sore Ears	42	0

ogists, the symptoms in Table II show that 67 per cent had sore eyes, 57 per cent had sore throats and 38 per cent had ear symptoms. One would wonder if many of our cases of catarrhal otitis media, aside from this definite group, are not viral in origin. We have hopes that we may have sufficient cases in the near future to present such a group.

CAT SCRATCH FEVER

One of the authors (P.E.I.) has had three private cases of cat-scratch disease, so became interested in the work being followed in the Medical Clinic of the Toronto General Hospital by Drs. G. Hart and W. Spaulding. In one year they have seen 40 cases, and it is with

their permission that we quote from their findings which are not yet published.

This disease, which is a benign condition, viral in origin, is important because it may mimic more serious causes of enlargement of lymph nodes. The features have been quite well described by Daniels[4] and Rosenblum.[5] The history is of a minor scratch or contact with a cat. This is followed by a local papule or vesicle at the site of the scratch. This incident may be forgotten, but several weeks later the regional lymph nodes enlarge with malaise and low-grade fever lasting up to several weeks. The lymph nodes become tender and frequently break down and show, on pathological examination, a chronic granuloma impossible to differentiate from tuberculosis, with a caseous type of necrosis and giant cells. The disease usually runs a benign course, but lymph nodes may remain enlarged for two years.

All but three of the 40 cases had close contact with cats. Twenty could recall a scratch from one to three weeks before the lymph nodes enlarged. Only three of the cats had shown any signs of illness, and one child had no contact with a cat, but had scratched his finger on a thorn bush.

Adenopathy. In 22 cases the epitrochlear and axillary nodes were involved due to inoculation by hand scratches; ten originated from the feet or legs, eight from pats or scratches of the face or neck giving cervical or preauricular nodes. The nodes become tender and adhere to the skin and adjacent tissue.

In 18 cases there was fluctuation; aspiration of purulent material failed in all to show on smear or culture pyogenic or tuberculosis organisms.

Differential Diagnosis. Infectious mononucleosis was considered in two patients, although mild fever, malaise, sore throat and enlarged cervical nodes may occur in this or cat-scratch disease, in the latter there is neither the characteristic changes in the blood smear nor a positive Paul-Bunnel test. Tuberculosis was diagnosed in four patients on the biopsy reports and two of these were admitted to a sanatorium. In each of these cases the tuberculin test was negative, the chest x-ray normal, prolonged fever was absent and no tubercle bacilli was found on the smear, guinea pig inoculation or culture. The findings in five cases were originally attributed to Hodgkin's disease and two others were clinically thought to be tularemia. In

one case the diagnoses considered were syphilitic chancre of the lip, with adenopathy or the malignant pustule of anthrax. Rheumatic fever was considered early in one case, because of erythema nodosum and a palpable spleen.

Skin Test. The cat-scratch skin test is done by injecting 0.1 cc of an antigen of known potency intradermally, noting the local reaction after 48 hours. A positive reaction consists of a papule of at least five mm in diameter and an erythema of at least 10 mm in diameter.

Only 38 of the 40 patients were so tested, and all gave positive responses with potent antigen. Three of these at the time of the test had tenderness, enlargement of lymph nodes or recurrence of discharge from a pre-existing sinus, suggesting a transient exacerbation of the inflammatory process. Fourteen successive healthy controls were all negative. There were also 12 patients tested with conditions such as leukemia, carcinoma, lymphoma and Herpes zoster with negative results. One patient (not included in the series) clinically had cat-scratch disease, but a negative test. He was receiving cortisone therapy.

The test seems to be a very good criterion for the diagnosis of the disease in the general population. McGovern[6] found 4 positive tests in 18 employees in an animal hospital and 10 per cent in healthy control subjects. This latter figure seems much too high for our area. Also one of the present series gave a positive reaction eight years after his illness. The test, therefore, must be associated with the clinical findings and resembles the tuberculin reaction. The big exception is that a very small percentage of the population will react to the cat-scratch antigen.

SUMMARY

Cat-scratch disease is not rare, although only recently recognized as an entity. It can present a confusing diagnostic problem if we do not recognize its clinical course. The skin test is a most useful clinical adjunct and is usually negative in healthy people or in other similar diseases. Suppuration in cervical glands in the absence of tubercle bacilli or pyogenic organisms should make us suspicious of this disease especially when the biopsy is reported as tuberculosis. The disease is usually benign and self-limiting and aspiration of fluctuant glands is all that is necessary. A few deaths have been reported from encephalitis so that we must always wonder if epidemic forms of this virus disease in a more severe form is a possible threat. All antibiotics are

ineffective for treatment. Cortisone may have an inhibitory effect, but there seems no need to use this potentially dangerous drug in this benign condition.

REPORT OF CASES

CASE 1. Miss X, aged 23. This German immigrant girl was working as a secretary. She developed first a papule, then a larger pustule below the margin of the mandible at the submaxillary gland area. In about eight days glands developed in the submaxillary area, and the anterior cervical chain. Anthrax was thought of but aspiration showed the fluid sterile for organisms. Skin tests were positive for cat-scratch fever. At the onset she had malaise, fever and sore throat. She had been given all the old and newer broad spectrum antibiotics with no effect. At her boarding-house a cat met her each night and jumped from the newel post to her shoulder, patting her face affectionately, but never scratching her. The owner of the house had also a history of pustules on his legs, and had tender inguinal glands. He was positive also for cat-scratch antigen in a skin test.

CASE 2. Miss G., aged 24. This girl was employed as a research chemist with no immediate contact with cats. She was seen by one of the authors last June with a firm mass about 2.5 cm in diameter in front of the right ear. This mass seemed free from the skin, but firmly anchored to the deep structures. With a history of at least a year, it was thought to be a parotid tumor, and arrangements were made to remove it in September. Her father was a doctor, but she was away from home and when she appeared for operation there was a fluctuant mass. This was removed and found to be broken-down lymph gland with parotid tissue also attached to the deep surface. Smear and cultures failed to show pyogenic organisms or tubercle bacilli. Pathologically there was a typical caseous necrosis with tubercle-like formation, and giant cells. No organisms could be found in the tissue by acid-fast stain. She was repeatedly tested and found negative by tuberculin, but positive to cat-scratch antigen. The area healed, by first intention with no recurrences or evidence of other gland involvement. She had visited on a farm where there were cats, but that was the only contact found.

VIRUS DISEASE IN ANIMALS AND BIRDS

We were very much enlightened to find, on a visit to our Ontario Veterinary College, the familiarity they have with this type of disease

in animals. It is recognized in the distemper of dogs, epidemic encephalitis of horses, swine rhinitis, turkey sinusitis, psittacosis and many other strains in fowl. They not only have been able to isolate many of these viral strains, but to grow them and transmit them to other animals with the reproduction of the clinical disease.

The most striking of the group, from our point of view, is the turkey sinusitis. This has been mentioned by Dr. C. E. VanRooyen. This disease produces marked distention of the sinuses. The causal agent has been cultivated in embryonal egg media, and the disease reproduced.

We have recently become interested in a local problem of human infections related to fowl disease, but so far the findings are most incomplete. In A———, a town of about 5,000 population, the local practitioner began to find an enormous number of so-called atypical pneumonias of short duration which he chose to call virus pneumonia. There occurred 304 cases in a period of four months. He kindly gave us his records and one of the authors (T.M.) has gone over these carefully. There is no true clinical picture in the symptoms listed that could be called a disease entity. There is a history of a sore throat, varying up to two weeks before the onset of severe general malaise, frontal and suboccipital headaches and patchy rales present on chest examination. On inquiry from a number of these patients they have stated that they felt quite ill for about three days. Unfortunately for the diagnosis of a virus infection, they recovered on the broad spectrum antibiotics—usually aureomycin.

To the local practitioner there occurred the thought of two possible sources of these infections. These were the enormous number of pigeons around the town and the fact that 30,000 turkeys were raised within a five mile radius. On two separate occasions batches of apparently healthy pigeons were submitted to the Provincial Laboratory to check for psitticosis. In the first group 30 per cent showed a positive reaction, the second group showed 60 per cent. This latter group shows a much higher percentage than is usually found in the pigeon population and is certainly suspicious of an outbreak of disease in this group.

From April, 1954, blood was submitted from 102 patients for agglutination tests for virus infections. The method of taking the specimens was 1) at the onset before treatment was initiated, 2) after treatment, or two to three weeks after the onset of the disease. Of

these, 68 agglutinated with influenza A.A.—one or B; 21 agglutinated with psittacosis. Unfortunately most of these were one in ten to one in twenty, which is of no significance. Only two cases showed significant figures—1 in 10 to 1 in 160, and 1 in 160 to 160. One is forced to state that the findings are of no significance in regard to psittacosis as a causative agent.

We can not help but feel that the clinical judgment of an older practitioner must be respected and not turned down by the failure of laboratory procedures. This type of semi-epidemic acute respiratory disease certainly did occur in this town, and not in adjacent towns. The physician has plotted the density of his cases on a map of the area which shows a marked density of the cases in the areas nearest the concentrations of turkeys and it is most striking in appearance. We are hoping to find a virus in the turkeys, perhaps similar to that giving turkey sinusitis, which has been transferred from the turkey droppings to the human to produce the clinical picture.

SUMMARY

An attempt has been made to discuss virus diseases as a clinical problem. Too often we are assailed with such technical details of groups, strains and numbers that we become just more confused. In order to avoid this a good deal of exact technical information has been purposely omitted from this paper.

We do know that we have a problem in the general group of A.P.C. viruses. While conjunctivitis is the outstanding symptom we still have sore throats and catarrhal otitis media. We hope to show at a later date that, apart from this epidemic disease, many of our catarrhal otitis cases may also be of viral origin.

Cat-scratch fever is a new entity that should be in our minds in unusual adenopathy and can be diagnosed by a specific skin test.

Many problems of the acute respiratory diseases are a challenge to us. One of these in a local community has been presented. The problem of the common cold is perhaps economically the most unsolved of these challenges which must be met.

100 COLLEGE STREET

I wish to thank the Department of Ophthalmology, the Department of Bacteriology, and the Department of Medicine for their ever present co-operation.

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XXXVI

THE VIRUS THEORY OF NASAL POLYP ETIOLOGY AND ITS PRACTICAL APPLICATIONS

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Virus pathology is generally characterized[1] by either proliferation or degeneration of cells, or a combination of the two. In this connection Rivers[1] has remarked: "If the action of a virus is not extremely rapid and explosive, and if susceptible cells are capable of multiplication, the primary effect of the active agent is stimulation leading to cellular hyperplasia." No rhinologist questions the fact that hyperplasia has occurred when polyposis exists in the nose or sinuses. That an alteration in the dimensions of a given polyp is not entirely dependent upon changes in contained edema fluid is evidenced by the fact that a pathologist is unable to determine polyp size from an ordinary microscopic section.

The tendency toward slow or rapid recurrence of nasal and sinus polyps after excision, their spontaneous appearance and disappearance with the onset and subsidence of head colds in certain patients, and their slowness or absence of recurrence after diathermy needle coagulation cauterization of the postexcision stumps, united to suggest the possible viral etiology of these polyps. It was reported in 1950 by Weille[2] that viral infection seems important in certain allergic states. If this observation is correct, then the hypothesis of a viral etiology for polyps merely elaborates upon the present widely accepted relationship in many cases between polyposis and a background of bacterial allergy. There is no real conflict between those insisting upon allergy as a causative factor and the possible virus etiology under discussion.

It was decided to test the hypothesis by an experimental study of nasal polyps excised in routine office or hospital practice for the

From the Virus Laboratory of the Massachusetts Eye and Ear Infirmary.

possibility of a contained viral agent. It was fully appreciated that the mere presence of such an agent might be of great or of negligible importance in the puzzle of polyp etiology, but its absence, as determined by intensive study, would be strong evidence against the theory herewith proposed.

The clinician who so frequently tells a patient "you have a virus infection" often does so without the use of a virus laboratory. He may not be aware that even highly-trained bacteriologists must specialize in viral techniques before working in this field. The polyp etiology problem, as outlined above, was investigated in the bacteriology laboratory of Harvard Medical School over a two-year period by two workers approved by the chief of that department, Dr. Mueller. The first year was fruitless. Then Dr. Robert S. Gohd of that same laboratory, and later Director of the Virus Laboratory of the Massachusetts Eye and Ear Infirmary, undertook the study and accumulated a wide variety of data, some of which was "positive."

POSITIVE EXPERIMENTAL FINDINGS

Since a virus is always a total parasite in that it can multiply only by living a literally borrowed life within a cell, it was necessary to choose an experimental animal, preferably one which is both abundant and cheap. The chick embryo was decided upon because: a) it has been used successfully in the propagation of a large number of viruses; b) it is very sensitive to alterations in its metabolism; c) there is no development of antibody in the egg which would complicate and handicap the isolation of an infectious agent. Therefore an exhaustive study of the effect of nasal polyp suspensions on the fertile egg was undertaken. The first of several procedures to be tried was inoculation of the chorioallantoic membrane of 13 day old embryos with 0.1 cc of 10 per cent polyp suspension. Negative controls consisted of the same material heated to 60°C for 30 minutes. Every second day two controls and two test eggs were examined. The embryonic membranes; the allantoic, amniotic and yolk sac fluids; and the embryo tissues were observed and their appearance recorded. In addition, the fluids were tested for red cell agglutinins. The embryonic membranes were examined for cellular inclusions as were the heart, liver, lung, spleen, stomach, intestines and mucous membranes of the pharynx. A search was also made for gross changes in these structures, as well as for anomalies in the embryos. In addition to these experiments, all classic routes of chick embryo inoculation were

tried, including allantoic, amniotic, and yolk sac routes in 8-14 day old embryonated eggs.

A technique for the non-specific chemical detection of viral alterations of the allantoic membrane has been reported by Kilbourne and Horsfall.[3] This permits the recognition of viral infection by measuring the increased protein concentration of the adjacent allantoic fluid, and seems ideally suited for isolation of an unknown agent. Nonspecific false positives can be circumvented by the use of younger embryos or by dialysis of the test fluids.

Kilbourne and Horsfall found that after infecting the allantoic membrane by influenza virus, large amounts of protein could be demonstrated in the allantoic fluid. This was done by precipitation of proteins in the fluid with 10 per cent trichloracetic acid and assessing the resulting degree of turbidity in the spectrophotometer.

TABLE I.

RESULTS

EGG NUMBER	POLYP	SALINE
1	320	120
2	350	60
3	370	90
4	400	90
5	330	160
6	350	140
average	353	110

Our early experiments indicated that there were precipitable substances in normal allantoic fluid of 13-day embryos, whether inoculated with saline or uninoculated. This was different in character from a protein precipitate, but could not be differentiated from the latter by a turbidometric method. But by using 9- or 10-day embryos, with fluid for testing available at 11 or 12 days respectively, very little of the nonspecific interfering material appeared. Dialysis against ten volumes of saline removed it, suggesting it to be a small molecule (in contrast to large protein molecules).

Polyp extracts have been inoculated into these younger embryos and a considerable amount of protein has been found in the allantoic fluid 48 hours following the inoculation. The results are clear-cut. In a typical experiment the following values were obtained for the

optical densities of the turbid solutions (the optical density being also directly proportional to the protein concentrations[3] up to 500 turbidity units):

In this experiment there is about three times as much protein or precipitation material in polyp-inoculated eggs as in the controls. In studies with known influenza virus (Lee strain) it has been found possible[3] to centrifuge over 99 per cent of the viral agent out of the infected allantoic fluid with a reduction of only about 20 per cent in turbidity readings. Host reaction to the virus infection is believed to explain the increased protein, and a correlation may be drawn between the toxicity of the viruses studied by Kilbourne and Horsfall and the degree of protein increase.

If the cause of increased protein in allantoic fluid is due to a virus, then this effect should be transmissible. For example, a small amount of the polyp preparation is inoculated into several eggs. After a suitable incubation period, allantoic fluid from each egg is harvested, assayed for protein content and then pooled. This allantoic pool is called the first passage. A small amount of the pooled fluid is next inoculated into a second group of eggs and the eggs handled in a similar manner. Pooled allantoic fluid from the second group of eggs is called the second passage. If after several passages, a small amount of material from a previous passage still induces an effect in a subsequent passage, then the effect is a transmissible one and this property of transmissibility is a property of viruses.

The factor responsible for the increased protein in allantoic fluid appeared to be transmissible. Thus, material from the original polyp was passaged in a serial manner five times. A second and a third line were started with two additional polyps. The third line was carried to the ninth passage and the second to the sixth passage. One disturbing feature of the transmission experiments was the loss of virulence of our agent with successive passage in eggs. This was manifest at first in a failure to infect all eggs; and finally in a complete loss of activity. The first line of polyp material went through five passages infecting five out of six eggs in the last passage. The second line became completely inactive for eggs at the eighth passage. Three out of six eggs were infected at the sixth passage, two out of six at the seventh and none of six were active at the eighth passage. Three of six eggs were positive at the level of the ninth passage of our third line.

COMMENT

Basic experimental research is often fruitless, frustrating, and time-consuming in terms of years of effort. So little progress has been made in the past relative to polyp etiology that any encouraging experimental data deserve thorough exploration.

Our results are encouraging, but can be considered no more than suggestive. Huebner[4] and others have pointed out that the isolation of a viral agent from the nose and throat is insufficient evidence to implicate that agent etiologically with any given disease. Criteria modeled after Koch's postulates are required[4] for etiologic significance; Topley and Wilson[5] quote these as follows:

1. The organism should be found in all cases of the disease in question, and its distribution in the body should be in accordance with the lesions observed.

2. The organism should be cultivated outside the body of the host, in pure culture, for several generations.

3. The organism so isolated should reproduce the disease in other susceptible animals.

Attempts by us to produce gross or microscopic tissue changes in the nasal mucosa of experimental animals or in chick embryos have failed. However, the presence of a specific antibody concentration in the serum of polyposis cases, and its absence in controls, might be considered legitimate and important evidence. We hope to devise a serological test for exploring such a possibility. Immunological neutralization experiments with the Kilbourne-Horsfall chick embryo method may prove illuminating also.

If polyposis be considered of virus etiology, granted that the evidence for such is not fully proven, then certain clinical conditions may be explained at least partially.

1. Recurrence of nasal and sinus polyps and polypoid degeneration after surgical excision would be explained by simple proliferation of residual intracellular viral infection.

2. The gradual slowing down or absence of post-surgical recurrence, when diathermy needle coagulation of residual stumps of polyps or polypoid degenerative membrane is used, would have a rational basis. By such coagulation the tissue is "boiled" by the needle, and an hypothetical intracellular viral agent is destroyed.

3. Virus protein or virus infection in nasal and sinus polyps and polyposis may be important in the etiology of intrinsic asthma, vasomotor rhinitis, and allied conditions. If so, it is suggested that simple loss of virulence of the viral agent may be accompanied by improvement in the clinical condition. This is called a "spontaneous remission" in medical literature.

4. Adrenal steroid therapy in polyposis, as elsewhere, cuts down protein synthesis[6] about 50 per cent. This would strongly restrain a viral agent inducing cell proliferation since the virus and the cell compete with each other for the cell enzyme systems required for building materials. Alterations in extracellular edema fluid probably depend upon the vasoconstrictor action[7] of these compounds, a phenomenon unrelated to the presence of intracellular viral infestation.

5. The work is sufficiently encouraging to warrant experiments along related lines to search for a viral etiological agent in other types of benign tumors, such as laryngeal papillomata; the same may be said of malignant tumors.

Just what agent have we found? The following list enumerates some of the viruses that may be found in the nose or throat at the time acute manifestations of disease are present:

1. Common cold
2. Influenza viruses (A, B and C)
3. Primary, atypical pneumonia
4. Adenoidal-pharyngeal-conjunctival agents
5. Herpes
6. Poliomyelitis
7. Measles (and abortive measles)
8. Rubella (German measles)
9. Mumps
10. Pox viruses: chicken pox, small pox, vaccinia
11. Psittacosis
12. Q fever

It is unlikely that the virus present in nasal polyps will be identified as a member of the above list, but instead is probably a new addition. Kilbourne and Horsfall[3] have said: "It is conceivable that a virus might be recovered and identified immunologically as the

etiological agent of a disease solely by chemical evidence of infection of the chick embryo."

SUMMARY AND CONCLUSIONS

In summary, a virus as the etiology of the nasal polyp is highly plausible. The work cited has shown that polyp suspensions are capable of inciting chemical changes in the allantoic fluid of the chick embryo leading to increased protein in that fluid. This phenomenon is capable of being serially transmitted for at least five passages. The incitant, following filtration, retains almost all of its activity. These factors considered together suggest a possible relationship between virus and nasal polyposis.

However, attempts to produce gross or microscopic tissue changes in the nasal mucosa of experimental animals or in chick embryos have not been successful.

247 COMMONWEALTH AVE.

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The Scientific Papers of the American Otological Society

XXXVII

MICROSCOPIC STRUCTURE OF THE UTRICLE

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The histological structure of the utricle has been well-known for many years. It is envisualized as a wide epithelial tube having a thickened macula at one end, covered by an otolithic membrane. The macula is composed of sensory and supporting cells. The former are usually identified with those of the organ of Corti as "hair cells" of apparently similar structure. Only a few investigators have attempted to demonstrate some specialized areas or cells. Werner[1] noted the differences in the height of the hair cells and subdivided the macula on this basis. Von Fieandt and Saxen[2] pointed out certain unusual features in the cells surrounding the maculae of the otolith organs and the cristae and described them as secretory cells.

It seems doubtful that the utricle is the simple structure that is usually described, and indeed, physiological evidence has been presented indicating a variety of activity within the macula. Mygind[3] postulated subordinate and dominant parts. Tait and McNally[4] reported different responses to a slow and quick tilt. Lowenstein and Roberts[5] concluded there were several differently responding sensory endings present. Furthermore, it seems logical to assume the presence of some specialized cells outside the sensory area for the production of endolymph, yet no conclusive evidence for these has been presented.

It was believed that studies at higher magnifications might solve some of these problems. Wersall, Engstrom and Hjorth[6] have re-

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cently reported a preliminary study of the macula in which they described an unusual disposition of the nerve fibers. The present studies, made with the electron microscope have revealed further interesting details of cytological structure in both the macular and extra-macular portions of the utricle.

A brief review of utricular relationships in the vestibule, and the histology of the utricle will be given first before going over into the cytological details. In the adult, the utricle is a wide tubular structure with the semicircular canals opening into it. It is connected to the pars inferior of the membranous labyrinth only by means of a slender tube, the utricular duct. This duct forms one arm of a Y-shaped arrangement, the other being the saccular duct from the saccule. The two come together to form the endolymphatic duct which leads into the endolymphatic sac.

The cristae are arranged so that the ridge of each is perpendicular to the plane of the canal. The saccular macula is in a vertical plane. The macula of the utricle is parallel with the lateral canal. If the head is tilted slightly forward, the largest part of macula is then flat, although the anterior end is still curved upward. The macula lies on the floor of the utricle, so that in an upright position, the otolithic membrane rests on the hair bearing ends of the sensory cells.

THE MACULA

The macula of the utricle is wedge-shaped with the broad anterior end turned upward. It is overlaid with a gelatinous material into which the hairs of the sensory cells project. The otoliths are embedded in the free surface of the gelatinous substance. In the fixed, dehydrated, decalcified guinea pig ear, a thin, rather ill-defined layer can be seen situated over the hair cells, into which hairs project. There is a suggestion of included fibrils. It is never as well preserved as either the cupula or tectorial membrane, and it seems probable that the usual fixation and dehydration methods alter its character considerably.

Most investigators agree that the otoliths represent some form of $CaCO_3$. Recent studies by Carlstrom, Engstrom and Hjorth[7] have shown the otoliths from man, the rabbit and the guinea pig to be in the form of calcite. They noted the length of human statoconia to vary from 1 to 20 microns.

Fig. 1.—Electron micrograph of the macula of the utricle. Guinea pig. 1 micron indicated. The otolithic membrane is absent in this and all other micrographs. A tall hair cell and supporting cell are shown. C, cuticular plate; E.R., endoplasmic reticulum; H, hair cell; M, mitochondria; N, nerve; Nu, nucleus; R, reticular lamina; S, supporting cell.

Sections of the guinea pig macula viewed at magnifications of about 300 x show it to be composed of two types of cells, sensory and supporting, separated from a connective tissue stroma by the basement membrane. The connective tissue layer contains the myelinated nerve fibers, arterioles and an extensive capillary network.

The supporting cells rest on the basement membrane and their nuclei can be seen in a row just above it. A slender column extends

up from a large base to the surface of the macula where their apical ends form the reticular lamina.

The hair cells, which are interposed between the supporting cells are of two heights. The taller cells are flask-shaped, with a rounded base, slender neck and widened apex. Their nuclei are obvious above those of the supporting cells. The row of nuclei seen closer to the surface belong to the shorter, more bulbous cells. Only the short cells are found at the periphery and in a shallow medial groove described by Werner.[1] Elsewhere, although the total height of the epithelium may vary, both short and tall cells are seen.

METHODS

The labyrinths of three guinea pigs were fixed in Dalton's fluid.[8] This was accomplished by perfusion of the osmic acid "in vivo" so that the fixative filled the perilymphatic scalae of the cochlea and vestibule. The animals were then decapitated, the temporal bones removed and immersed in the fixative for a total fixation period of one hour. The ears were washed for forty-five minutes in three changes of distilled water and left in 70 per cent alcohol overnight. The utricle was dissected free from the bony vestibule. If the otolithic membrane had not already fallen away, it was removed at this time, as it was found to be difficult to obtain good sections with the crystalline membrane in place. Rapid dehydration through the alcohols was accomplished, and the specimens embedded in a methacrylate mixture (1 part methyl + 8 parts butyl, or 1 part methyl + 3 parts butyl) in gelatin capsules. (The technical details have been described in a paper concurrently in preparation.[12] Sections were cut by means of glass knives in either a Porter-Blum or Minot Rotary microtome. Thicker sections (1 to 2 microns) were utilized for studying utricular structures at lower magnifications. Thin sections (1/20th of a micron) were used for viewing in the RCA electron microscope, model EMU 2E. Photographs were made at original magnifications of 1900x to 10,550x. Micrographs were printed at enlargements of 4x or greater.

OBSERVATIONS

1. *The Supporting Cells.* The plasma membrane of the supporting cell is a delicate, osmiophilic membrane with few indentations. At the base of the cell, it is separated from the underlying connective tissue by the basement membrane. It is closely applied to contiguous

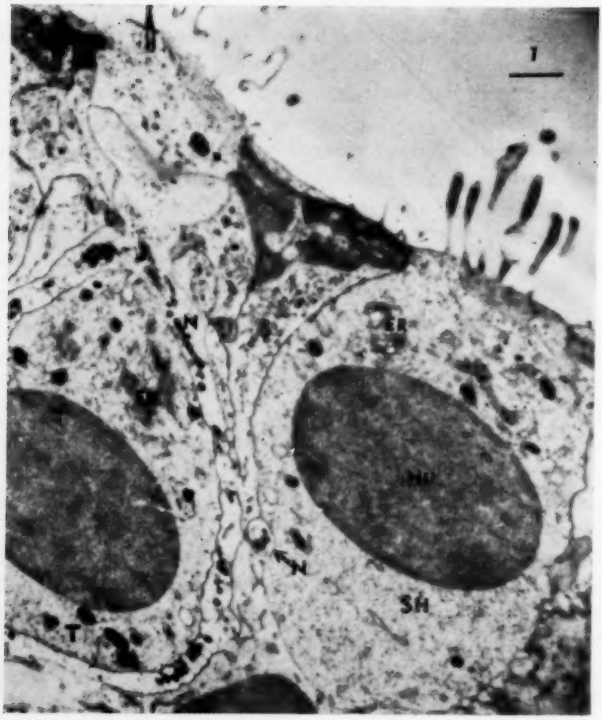

Fig. 2.—Electron micrograph showing the two types of hair cells in the macula of the utricle. Guinea pig. 1 micron indicated. A tall cell is on the left, a short cell on the right. Note the aggregates of endoplasmic reticulum in the supranuclear part of the cells. E.R., endoplasmic reticulum; N, nerve; Nu, nucleus; S, supporting cell; Sh, short hair cell; T, tall hair cell.

cell membrane, i.e., the hair cells, nerve and other supporting cells. At the apical end it continues up over the few microvillous projections present (Figs. 1 and 2).

The base of the cell is occupied by a large, round, lobulated, or pyramidal nucleus. The cytoplasm contains a light granular material. A few mitochondria, vesicles and beaded cisternae are seen in the base and slender column, but the cytoplasmic organelles tend

to be localized in the widened upper portion. Many membranous profiles are found here, ranging from small, round vesicles to long cisternae, some of which take irregular shapes. Their lumina are more osmic-dense than the surrounding cytoplasm. Some of the micrographs show these cells to have one or two aggregates of Golgi apparatus. Figure 1 shows several supporting cells with accumulations of small, round, osmiophilic bodies in their upper portions. These are of variable size and shape. Some rods are also evident. Other micrographs show similar bodies of much larger size, just below the plasma membrane at the upper cell surface. Some of these bodies are undoubtedly mitochondria. Others, which appear to have no internal structure and an irregular limiting membrane, are of indeterminate nature.

The osmiophilic material seen in the apices of all the supporting cells in Figures 1, 2 and 3 is the reticular lamina. Figure 3 shows it to be a dense, finely granulated material. It is separated from the plasma membrane at the free surface by a thin cytoplasmic layer. At the sides, plasma membrane and reticular lamina are indistinguishable. In Figures 1 and 2, the reticular lamina appears to entirely fill the cell apex, with only a few open communications between apical cytoplasm and the rest of the cell. Other micrographs reveal a large central area uncovered by the granular material. Apparently the reticular lamina occurs as a wide, peripheral circular band, but not completely filling the apex of the supporting cell.

2. *The Hair Cells.* Figure 2 shows two hair cells. The cell on the right has been sectioned approximately through the midline, the other slightly off center. The plasma membrane is a thin, osmiophilic layer showing some irregularities in outline. Indentations are occasionally made by contiguous nerve fibers. The plasma membrane of the hair cell is closely adherent to those of neighboring cells and free areas are rarely seen. At the cell apex, the membrane is thickened and more osmiophilic where it contacts the reticular lamina of adjacent supporting cells (Fig. 3).

The hairs, seen in Figure 3, are covered by an extension of the plasma membrane, which appears thickened. They are filled with a dense granular material which extends as a short root downward through the cuticle to the more diffuse cytoplasm. The peculiar curled appearance of some of the hairs in Figures 2 and 3 is undoubtedly dissection artefact.

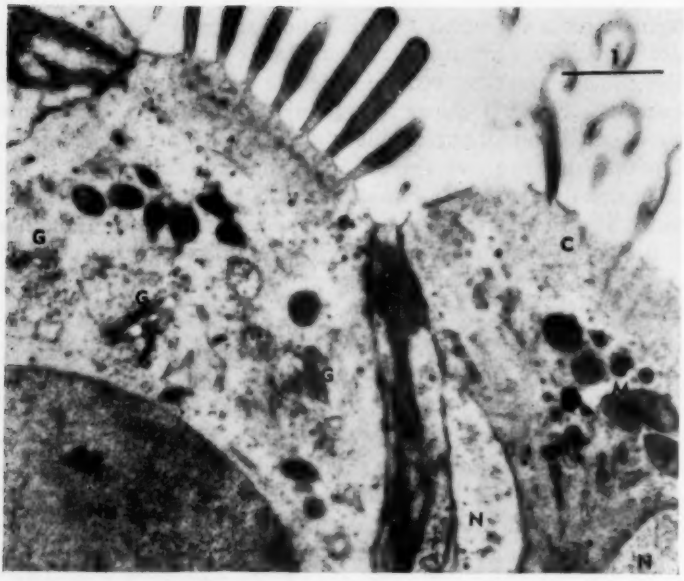

Fig. 3.—Electron micrograph showing cytological details of two hair cells. Guinea pig. 1 micron indicated. The size and shape of the endoplasmic reticulum ranges from small vesicles to large cisternae. Three aggregates of smooth membranes (Golgi apparatus) are visible. C, cuticular plate; G, Golgi apparatus; M, mitochondria; N, nerve; Nu, nucleus.

The nucleus is large and round. It is invariably found in the bulb of the cell.

The cytoplasm is finely granular throughout the entire cell. A slightly more dense material, the cuticle, covers the apical end. Figure 2 shows several large cisternae of irregular shape in the infranuclear cytoplasm. Figure 4 shows the base of a hair cell at higher magnification. In this cell, the endoplasmic reticulum takes the form of small, round vesicles as well as some larger, sometimes irregular cisternae. Three elongated cisternae, in parallel arrangement, are found just below the nucleus. The density of their lumina varies, but is usually higher than that of the cytoplasm. These membranes appear to be of the granular type. The cytoplasmic matrix surrounding them is

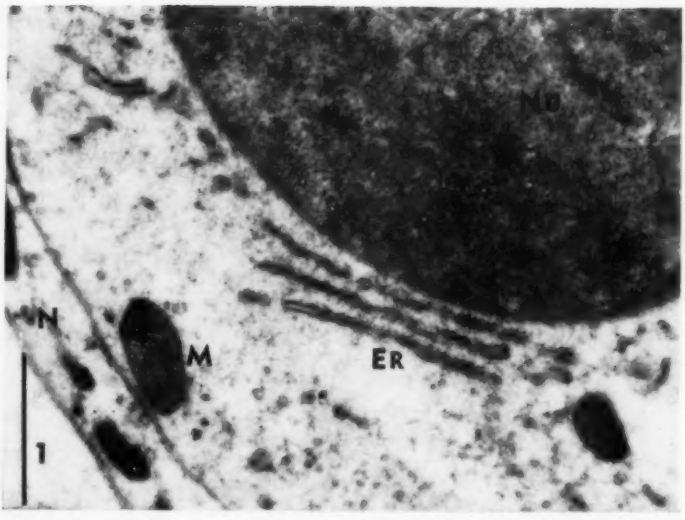

Fig. 4.—Electron micrograph of the basal portion of a hair cell showing the parallel arrangement of the endoplasmic reticulum. Guinea pig. 1 micron indicated. E.R., endoplasmic reticulum; M, mitochondria; N, nerve; Nu, nucleus.

more dense than elsewhere. The cisternae closest to the nucleus seems to be longest, as discontinuous strands can be observed to follow the nuclear membrane to the left. Similar parallel membrane orientations have been found in other hair cells, but only below the nucleus.

The supranuclear cytoplasm obviously contains more formed structures. The cell in Figure 3 shows membranous structures of varying shapes and sizes, with small round vesicles predominating. Three of the aggregates of smooth membranes which are usually described as Golgi apparatus are visible. Two large globules with small vesicles both inside and out can be seen to the right.

The mitochondria show typical internal cristae and limiting membrane. They are large and scattered throughout the cell. Some demonstrate osmiophilic bodies, a feature which seems to be more prominent in the apical organelles.

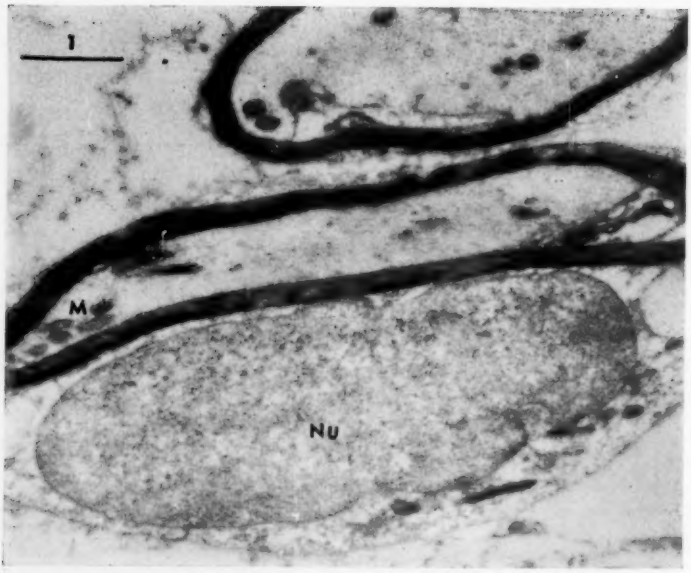

Fig. 5.—Electron micrograph of myelinated utricular nerve fiber in connective tissue below macula. Guinea pig. 1 micron indicated. The myelin sheath is seen as concentric electron-dense lamellae surrounding the axon. The nucleus (Nu) of the Schwann cell takes up most of the cytoplasm. The axoplasm contains mitochondria (M), a fibrillar material, and a few small vesicles.

3. *Nerve Fibers.* Figures 1 and 2 show some of the hair cells to be completely encircled by a thin cellular layer which widens around the neck of the cell and terminates just below the reticular lamina. Study of the cytological details of this layer and comparison of the micrographs with other sections of the macula stained by silver impregnation methods forces one to the conclusion that this is the vestibular nerve terminus.

The precise pattern of the hair cell innervation is difficult to determine. The hair cells in Figure 1 and that on the left in Figure 2 show the cells to be completely encircled from base to neck by a continuous layer of axoplasm. This widens out at the neck, making a

sort of flared collar on which the hair bearing end of the cell rests. It seems probable that the nerve axon widens considerably as it contacts the hair cell membrane, but it seems unlikely that a single continuous sheath completely surrounds the cell. It is hoped that further studies will clarify this point.

Many of the hair cells show an entirely different pattern of nerve distribution. The hair cells in Figure 2 right, and Figure 7 show only a few, small contiguous nerve fibers. The nerve at the base of Figure 7 gives the impression of an ascending spiral that ends at the lower left. The nerve ending shows the thickened synaptic plate and accumulation of small vesicles and mitochondria that have been described for other synapses.[9,10,12]

It may be that there is no distinction between the innervation of different cells and the different micrographs merely show sections at a different level. However, the micrographs almost invariably show the tall, columnar cells to have the encircling fibers, while the short, blunt cells are more diffusely innervated.

The changes in internal characteristics of the nerve fiber can be noted in micrographs taken from different locations. The myelinated fibers of the utricular nerve found in the connective tissue stroma are seen in Figure 5. The nerve axon is surrounded by the myelin lamellae and enclosed by the Schwann cell. The axoplasm is filled with a wispy fibrous material. Several mitochondria and a few small round vesicles are present. In the lower left of Figure 6, two nerve fibers are visible in the supporting cell layer. No myelin or Schwann cell sheath is present, but the nerve axon shows little change from that in Figure 5. The portion of the nerve fiber at the base of the sensory cells shows less fibrous material and an increasing number of small vesicles and mitochondria. Figures 1 and 3 show the terminal at the neck of the cell to be composed mainly of the small round vesicles. Most of the mitochondria are found in that part of the fiber adjacent to the bulbous portion of the cell.

The plasma membranes of nerve fiber and hair cell are closely adherent. A definite thickening of the membrane, such as is usually described for synaptic areas, is not evident. However, the union of nerve and sensory cell membranes does seem to be more electron dense that other adjacent cell membranes (Figs. 1 and 6).

4. *Body of the Utricle.* The extra-macular portion of the utricle (the body) is composed of a low epithelial layer, overlaying a

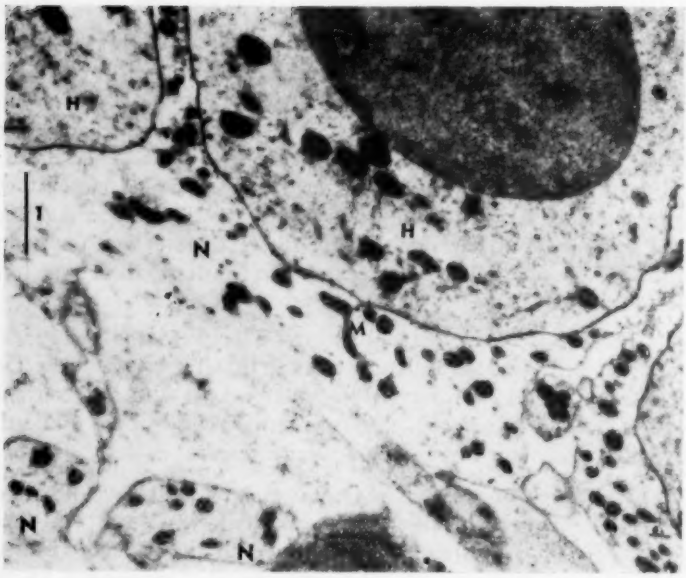

Fig. 6.—Electron micrograph showing the changing character of the axoplasm. Guinea pig. 1 micron indicated. The two unmyelinated nerve fibers at lower left are entering the macula. An increasing number of vesicles is apparent in the fibers near the hair cells. H, hair cell; M, mitochondria; N, nerve.

loose connective tissue. The epithelium may be rectangular in shape, resembling the cells of Reissner's membrane, or more cuboidal in outline. The plasma membrane is smooth and straight at the endolymph surface without microvilli (Fig. 8). The plasma membrane of adjoining cells is closely adherent at the endolymph surface giving the appearance of a system of terminal bars. Contiguous cell membranes may be straight or show a few of the interdigitating processes commonly found between adjoining cells. The base of the cell is separated from the underlying connective tissue by a thin, but distinct, basement membrane. The nucleus is large and oval. The cytoplasm is lightly granular and contains mitochondria and a sparse amount of endolymph reticulum. The latter is in the form of small vesicles and short cisternae. Large, round globules, with clear centers and small

vesicles both inside and out (such as those described in the hair cells) are frequently encountered in the supra-nuclear portion. The base of the cell is often straight, but some interdigitations between plasma and basement membranes may be present.

The above-described cells are found only in a part of the guinea pig utricle. In many places the whole appearance of the epithelial layer is considerably altered. This is effected by an extreme branching of a greater part of the plasma membrane and an increased cytoplasmic density. The change may be gradual with the basal plasma membrane acquiring an increasing number of projections, or it may be abrupt.

Figures 9 and 10 show the latter type of cell. The endolymph surface is smooth, without demonstrable microvilli. Adjacent cells are closely adherent only near the endolymph surface as shown in Figure 11. The remainder of the plasma membrane is tremendously increased by many long, thin branching processes. These are numerous enough to sometimes give a lamellated effect, but they are never so tightly packed as to exclude some visible interspaces. Their width is fairly constant, except where an entrapped mitochondrion causes a bulbous enlargement.

The space into which the processes project is limited below by the basement membrane. This latter is more or less parallel with the upper epithelial surface. Many of the processes abut upon it and some extend longitudinally along it. It is seen in Figure 10 as a thin, dark line somewhat less dense than the plasma membrane, but thicker. It is separated from the latter by a space of constant width and low density. The large spaces thus formed are apparently filled with fluid and extracellular. A fine granular precipitate is sometimes visible (Figs. 9 and 10).

The cytoplasm of the cells (Figs. 9, 10 and 11) is packed with a heavy, fine granular material which in some micrographs is only slightly less dense than the nuclear material. The endoplasmic reticulum appears to be sparse. A few membrane profiles can be seen in the projections in Figure 11. The mitochondria are large and may be present in the projections as well as in the upper part of the cell. Some large, clear globules are sometimes seen near the endolymph surface. These may conceivably represent the blind termini of sections of the fluid space.

Fig. 7.—Electron micrograph of a short hair-cell showing an ascending nerve fiber at the base and a nerve ending at lower left. Guinea pig. 1 micron indicated. N, nerve; N.E., nerve ending.

The nucleus in Figure 11 is oval with an indentation. Often the nuclei are lobulated or may be regionally compressed to conform to the limited cytoplasmic area available.

There is a distinct relationship between the subepithelial pigment cells and the branched epithelium. Figures 9, 10 and 11 show the pigment cells below the basement membrane. Furthermore, extensions of these protrude up into the fluid space and are there encircled by the epithelial fingers (Fig. 10). The areas where the connective tissue is free of pigment cells are overlaid by the rectangular or cub-

oidal epithelium. The extreme branching occurs only where the pigment cells are numerous.

DISCUSSION

It seems valid to class the sensory cells of the membranous labyrinth together as hair cells. They all show typical hairs which, while not demonstrating the internal structure of motile cilia,* are certainly more than just cytoplasmic extensions. Here the similarity ends. The utricular hair cell is revealed as being quite different in internal structure from the external hair cells of the cochlea. It shows nothing of the peripheral vesicular membranes and related mitochondria so prominent in the latter.[11] In some respects, it more closely resembles the internal hair cell.[12]

The two most prominent membrane features, the parallel cisternae and membranous collections known as the Golgi apparatus have been described for several specialized cells and it has been suggested by Palade[13] that they represent local differentiation processes. As these membrane modifications appear to be constantly located respectively below and above the nucleus, it seems reasonable to assume some differentiation of metabolic processes in the apical and basal parts of the utricular hair cell.

The hair cells with the closely applied nerve fiber demonstrate an unusual type of nerve ending. These were also noted by Wersall, Engstrom and Hjorth.[6] Herein lies another point of differentiation from the cochlea. While the nerve endings on internal and external hair cell are not altogether similar, they are found as enlarged knobs, restricted to the lower half of the cell.[12] It is difficult to know whether only the bulb at the apex of the utricular hair cell should be termed "nerve ending" or whether the entire hair cell-nerve fiber contact surface may be of physiological significance. It seems probable that these cells may be considerably more sensitive to slight deformation than if the nerve endings were localized to the base. Further, the manner in which the wide cell apex rests on the nerve bulb suggests that not only the hairs, but also the head of the cell may be sensitive to pressure differences.

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*NOTE: Wersall has recently reported the presence of one kinocilium on each hair cell of the crista. Wersall, J.: Studies on the Structure and Innervation of the Sensory Epithelium of the Cristae Ampullares in the Guinea Pig. Acta Oto-laryng. Supp. 126, 1956.

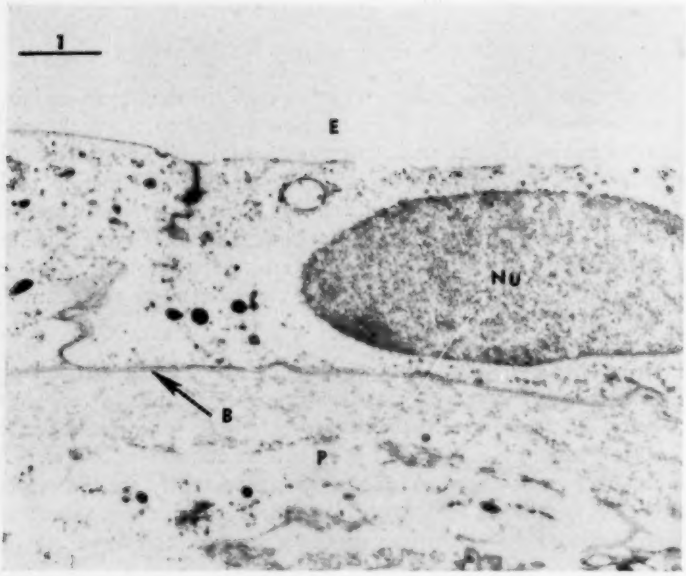

Fig. 8.—Electron micrograph of undifferentiated epithelium in the body of the utricle. Guinea pig. 1 micron indicated. B, basement membrane; E, endolymph; Nu, nucleus; P, perilymph.

A variety of responses from the otolith organ has long been postulated. Mygind[3] divided the macula into dominant and subordinate parts and believed the former to be associated with the taller cells. Investigators[14] utilizing the silver impregnation methods have indicated considerable variability in the nerve pattern. Lowenstein and Roberts,[5] in analyzing the electrical responses from nerve fibers in the lateral aspect of the dogfish utricle, concluded there were at least two different nerve endings present in this region. There are undoubtedly two types of cells in the guinea pig macula, one a tall columnar cell, the other a short bulbous cell. The present findings confirm those of Werner[1] that, at the periphery and in the narrow groove only the short cells are found. Elsewhere, the two types alternate. The internal structure of both appears similar. While these are only beginning studies, and the evidence is not yet conclu-

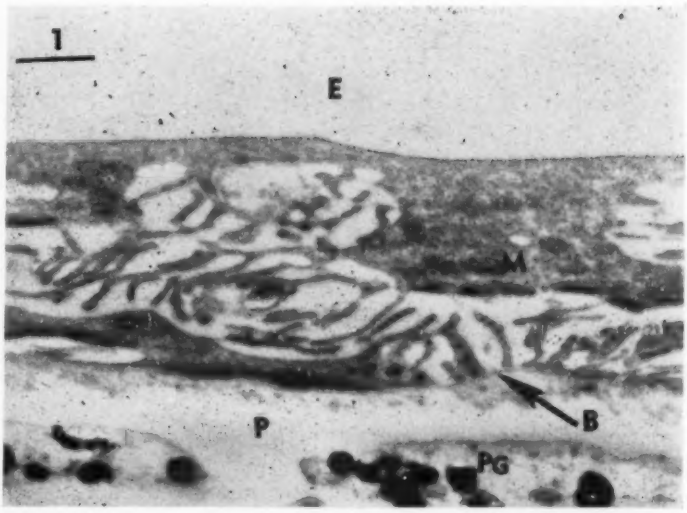

Fig. 9.—Electron micrograph showing the branched epithelium in the body of the utricle. Guinea pig. 1 micron indicated. B, basement membrane; E, endolymph; M, mitochondria; P, perilymph; Pg, pigment granules.

sive, the micrographs do indicate a difference in innervation. Almost invariably the taller cells show the encircling type of fiber, while the shorter cells are more diffusely innervated. It has not yet been determined if this difference is generalized, or dominates certain areas. It is hoped that further studies will elucidate the nerve configuration and distribution.

Wersall's findings in the cells of the crista ampullaris[15] studied by means of the electron microscope show several similarities to the present observations. He found two types of hair cells to be present in the crista likewise. The infranuclear parallel membranes were described for one of these. Two types of innervation were also found: a nerve "cup" surrounding the flask shaped cells and more diffuse endings on the other cells. The supporting cells contained many granules, which may be similar to those in the macula. These findings indicate that the sensory areas of the vestibule may more closely resemble each other than they do those of the cochlea.

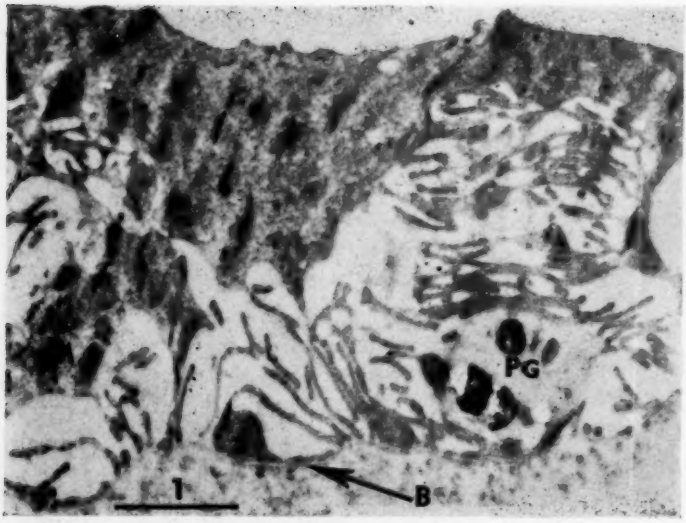

Fig. 10.—Electron micrograph showing branched epithelium of the body of the utricle. Note the pigment granules. Guinea pig. 1 micron indicated. B, basement membrane; M, mitochondria; Pg, pigment granules.

Probably the most interesting finding in this study has been the demonstration of the branched epithelial cells in the body of the utricle. They are not visible within the resolution limits of ordinary microscopy. Close examination of the utricular epithelial tube at low magnification does reveal areas where the cells appear extraordinarily thin and basophilic. But these might ordinarily be discounted as sectioning or staining artefact. Neither are these the circummacular cells described by von Fieandt and Saxen.[2] The cells in that location seem to be a continuation of the supporting cell layer with similar internal structure.

Two features are outstanding: first, that the basal plasma membrane is tremendously increased by the projections, and second, that large, clearly demarcated fluid spaces are created. These "pools" are separated from the trabeculated perilymph space only by the basement membrane, which gives the appearance of a more effective filter

Fig. 11.—Electron micrograph showing a branched epithelial cell at higher magnification. Guinea pig. 1 micron indicated. E, endolymph; M, mitochondria; Nu, nucleus; Pg, pigment granules.

than barrier. It may be of significance that the utricle is surrounded by a well-developed capillary network,[16] a somewhat surprising circumstance when the complete avascularity of Reissner's membrane is considered.

It would seem advisable to look for parallel structures in other organs that may give us some hint as to the significance of this area in the utricle. Branching epithelial cells have been observed with the electron microscope in the kidney.[17-19] The epithelium surrounding the glomerular capillaries sends out numerous processes which are attached to the capillary walls. It has not been postulated that these effect the passage of fluid from blood to urinary space, as other, more reasonable mechanisms for this process are present. The plasma membrane of the epithelium of the kidney tubules also shows an elaborate infolding with the formation of laminated projections. In the kidney also, the processes are limited by a basement membrane.

It is well known that the kidney glomerulus and tubules are well developed filtration structures. Some filtration or secretory region, for which no well-grounded evidence has thus far been given, must be present in the vestibular labyrinth for the production of endolymph. Such a tremendous increase in the cell surface area has usually been interpreted as indicating a corresponding increase in the passage of fluid across the cell membrane. However, the field of electron microscopy is too new to know how to interpret isolated observations. At least half of the membranous labyrinth has not been adequately exposed to electron microscopy, and it may well be that a neighboring area of even greater potentialities will be uncovered.

Until then, it can be said that here is a region of unusual function, one that bears watching. It can also be said that the utricle is not a simple structure, that cytologically, as well as physiologically, a variety of activity is indicated.

SUMMARY

1. Two types of hair cells are present in the macula of the utricle: short, bulbous cells, and taller flask-shaped cells.

2. The taller cells show long, encircling nerve fibers closely applied to the cell membrane. The shorter cells are more diffusely innervated.

3. The body of the utricle shows epithelial cells of unusual character in many places. These have numerous finger-like branching processes which project into fluid spaces, separated from the perilymph by a basement membrane.

4. The internal structure of the utricular hair cells does not show an organization similar to that found in the external hair cells of the organ of Corti.

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XXXVIII

THE IMPORTANCE OF THE OTOLITHIC ORGANS IN MAN BASED UPON A SPECIFIC TEST FOR UTRICULAR FUNCTION

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Of all our organs of special sense we know least concerning the otolith apparatus. The reasons are not hard to find. Anatomically, the otolith organs are not only remote but also intimately connected with other sensory structures in the inner ear. Physiologically, they cannot be stimulated independently of other sensory systems and their nervous pathways have not been traced to a specific "center" in the brain. Psychologically, it is difficult to evaluate their role in perceptual patterns and a specific sensation has not been ascribed to them. Functionally, they are not very important in our lives unless disease supervenes, whereupon they may be destroyed with little fear of handicapping the patient.

The advent of aviation has given a new importance to the otolith organs. The flyer, subjected to accelerative forces equatable with gravity, orients himself to the direction of this resultant force rather than to the direction of the earth's gravitational force. The otolith organs not only play a contributing role in this type of disorientation but also, under special circumstances, are solely responsible for troublesome illusions.[1-3] Morever, in the zero gravity state, a condition encountered when the flight path follows a parabolic curve or in flight beyond the earth's gravitational field, the absence of function or the abnormal functioning of the otolith apparatus may be important.[4]

These practical problems have served to focus attention on the utricle and have stimulated research at many places, including the

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From the Naval School of Aviation Medicine.

Opinions or conclusions contained in this report are those of the author. They are not to be construed as necessarily reflecting the view or endorsement of the Navy Department.

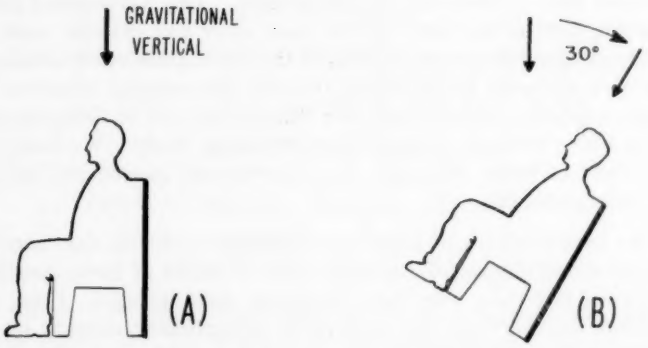
U. S. Naval School of Aviation Medicine. The experiments we have performed have all been carried out on man. This has imposed great difficulties, but in the final analysis man alone can provide some of the answers to our questions. Ideally, in the investigation of any sensory organ it is desirable to be able to control the essential stimulus, to measure a specific indication of such stimulation, and to compare men with and men without the sensory organ under study. We have had these ideals in mind although our experimental procedures include many compromises.

We have made use of a human centrifuge to provide the stimulus. This had the advantage of controlling the direction of linear accelerative forces, but there were two important disadvantages. First, the magnitude of this force was not under independent control, i.e., it was impossible to change the direction of force independently of the magnitude. Second, during the onset and cessation of rotation angular accelerations were also present.

With regard to a specific indication of stimulation to the otolith apparatus we utilized the oculogravic illusion[5] which will be described later on. That this illusion is the perceptual resultant of stimulation of the utricle is still an assumption although there is strong evidence that it has its genesis in the inner ear and that neither the cochlea nor the semicircular canal is essential.

Our subjects included healthy persons, patients who had recovered from unilateral labyrinthectomy,[6] and deaf individuals. The deaf were separated into those with and those without function of the semicircular canals, and the latter were separated into those who did and those who did not perceive the oculogravic illusion.[7] Although these separations were clear-cut, the number of subjects in the last two groups was small, and our work is far from complete. The difficulties in carrying out experiments on the deaf are not inconsiderable, and comparing results obtained from deaf persons with those obtained from healthy persons necessitates caution; the absence of sensory organs not only leaves blanks in perceptual experience but also stimulates compensatory adjustments.

The following report brings together some of our experimental findings and is divided into three parts. The first deals mainly with experiments carried out on a human centrifuge in which the subjects with eyes closed described their feelings of reorientation in space when subjected to a change in direction of resultant force. The second



NORMAL PHYSICAL CIRCUMSTANCES WHEN SUBJECT (A) SITS UPRIGHT AND (B) IS TILTED BACKWARD 30°.

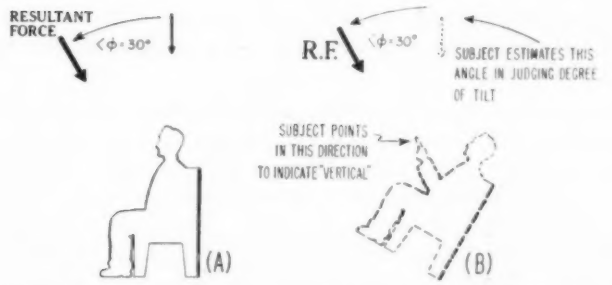
FIGURE 1

deals with the oculogravic illusion, a term applied to the visual aspects of reorientation to resultant force. The third part consists of a brief discussion of the significance of the otolith organs in man.

NON-VISUAL ORIENTATION TO FORCE OF GRAVITY AND TO ACCELERATIVE FORCES EQUATABLE WITH GRAVITATIONAL FORCE

When a person seated upright and with eyes closed is passively tilted backward, as shown in Figure 1, initially he is aware of the displacement and later of his new position with regard to the gravitational vertical. These phenomena are not only familiar experiences in the case of healthy individuals but also in the case of persons with unilateral and bilateral loss of function of the organs of the inner ears.

The question may be asked whether these experiences are the same in all subjects. If not, what differences are to be found? Our own findings suggest that there may be differences both qualitatively and quantitively, but our results are too meager to have validity.



(A) SHOWS THE PHYSICAL CIRCUMSTANCES WHEN A PERSON IS SUBJECTED TO A CHANGE IN RESULTANT FORCE RELATIVE TO HIMSELF WITH EYES CLOSED. HE FEELS THAT HE HAS TILTED BACKWARD (B) IN RELATION TO THE VERTICAL. ASKED TO INDICATE THE VERTICAL HE POINTS IN THE DIRECTION OF RESULTANT FORCE.

FIGURE 2

Highly sophisticated normal subjects describe what might be termed "after-effects" of tilting which are not reported by deaf subjects. Moreover, deaf subjects, especially those with loss of function of the otolith organs, are not very accurate in estimating the degree of tilt. However, all of these experiments require a degree of sophistication and attentiveness which is far less readily attained in the case of deaf than in the case of healthy subjects. The literature in this respect is somewhat confusing and does not provide definitive answers to these questions.[8-9,11-14,19]

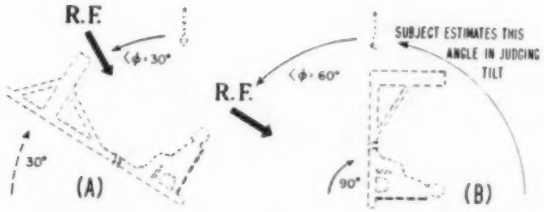
When a person with eyes closed is subjected to a change in direction of resultant force with respect to himself on a centrifuge, there are certain physical resemblances and differences when compared with tilting in a tilt-chair. The subject is passive in both instances, the change may occur in the same period of time, and the direction of force with respect to the body and supporting seat are identical (Fig. 2a). The chief differences consist in the greater magnitude of the force on the centrifuge and to effects incidental to the onset of rotation. However, with rotation at constant velocity the side effects disappear if the subject does not move his head. Every particle in the body is influenced by the resultant force in the same manner as

it was previously influenced by the force of gravity. The body as a whole accommodates to this force within the limits imposed by the supporting structures of the body and external restraint. Within the body the adjustments to resultant force are limited only by the rigidity of the tissues.

The subjects in all groups reported that they felt as if the seat and platform had tilted backward and that they had assumed a new position in space (Fig. 2b). However, the healthy sophisticated subject readily detects important differences between the experience on the centrifuge and in the tilt-chair. These differences can be divided into two phases, an initial dynamic phase followed by a static phase. There are two noteworthy features of the dynamic phase. First, a curious feeling akin to tingling pervades the entire body, resulting in an awareness that all portions of the body were actively participating in the change in bodily position. This feeling is a new experience and so characteristic that, once felt, it is not forgotten. The other noteworthy feature concerns the fact that the feeling of being tilted lasts longer than the period of time in which the change in resultant force occurred. For example, the change in direction of resultant force may take place in three seconds, but the feeling of being tilted may continue for another thirty seconds or longer, depending on the magnitude of the change. The feeling is that of being tilted at first rapidly, then slowly, until the final position of rest is reached. Typically there is no feeling of overshoot. The static phase begins when no further change is apparent. The feeling during this phase is much the same as in the tilt-chair except for the awareness of greater weight and pressing more heavily into the seat.

Much time and effort were expended in an attempt to determine if deaf subjects, with or without functioning otolith organs, experienced the lag phenomenon or the characteristic "tingling." The results were not clear-cut. The same subject would sometimes indicate a lag and sometimes not. All had difficulty in expressing their feelings. By their reports we could not distinguish between deaf subjects with bilateral loss of all functions of the inner ear and those with functioning canals and otolith organs. This suggested that we failed to indoctrinate them sufficiently and that lack of sophistication accounted for the unsatisfactory results.

Summary. Our findings indicate that healthy persons; individuals with one inner ear destroyed; and deaf subjects 1) with the nonacoustic labyrinths intact, 2) with the nonacoustic labyrinths destroyed, and



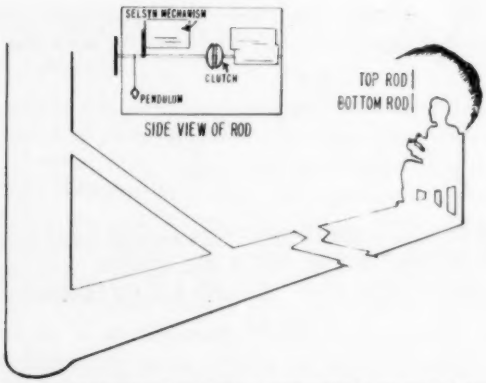
(A) ILLUSTRATES THE VISUAL ILLUSION EXPERIENCED WHEN A HEALTHY SUBJECT IS EXPOSED TO A CHANGE IN DIRECTION OF RESULTANT FORCE OF SMALL MAGNITUDE. WHEN THIS FORCE IS INCREASED ABOVE A CRITICAL LEVEL THE ILLUSION IS GREATLY EXAGGERATED (B).

FIGURE 3

3) with functioning otoliths but nonfunctioning canals readily orient themselves, even in the absence of vision, to the gravitational vertical and to changes in the direction of resultant force on the human centrifuge. Some investigators are not in agreement with this finding.[8,10] A peculiar feeling the healthy person experiences on the centrifuge is difficult to elicit from any of the deaf subjects. More extensive and intensive experimental study is needed to evaluate the role of the semicircular canals and otolith apparatus under these experimental conditions. Our experience points up certain difficulties in using deaf persons as experimental subjects and the need for caution in relying on passive tilt-tests for determining the function of the otolith organs.

THE OCULOGRAVIC ILLUSION

Experiments in a Lighted Room. When a healthy person with eyes open is subjected to a change in direction of resultant force relative to himself, he not only feels the reorientation of his body to this force but also objects in the visual field appear to move and to assume in space a new position which accords more or less with the direction of resultant force (Fig. 3a). This phenomenon, known since the time of Purkinje,[15] Mach,[16] and Breuer,[17] has been termed the oculogravic illusion.[5] Unsophisticated subjects consider the movement to be real movement. Sophisticated subjects are aware that relative movement does not occur, but this does not abolish the illusion.

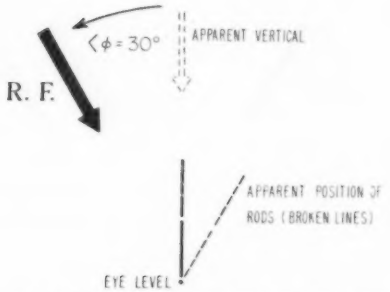


PHYSICAL CIRCUMSTANCES ON HUMAN CENTRIFUGE WITH SUBJECT VIEWING 2 LUMINOUS RODS IN THE DARK. INSERT SHOWS DETAIL OF ROD MECHANISM.

FIGURE 4

If the centripetal force is increased until the angle between the resultant force and the gravitational vertical is in the neighborhood of 60°, the illusion becomes more striking; the subject feels as if he were at right angles to the vertical. Moreover, he may feel that he is stationary and that the room is revolving around the centrifuge (Fig. 3b). Similar reversals have been reported by aviators during spins in which they seem to be stationary and the earth to be revolving around the airplane.

Experiments with Luminous Rods. A very useful experimental apparatus may be explained with the aid of Figure 4. This shows the subject seated under a canopy at the end of the centrifuge platform with his left side toward the center of rotation and facing in the direction of rotation. He is regarding two luminous rods in the dark. Each rod, as shown in the detailed sketch, is fastened to the end of a shaft to which is attached a pendulum. At the other end of the rod is a clutch and, by means of a solenoid, the operator can allow the rod either to remain free-swinging, in which case it assumes the position of resultant force, or he can fix the shaft, in which case it does not follow changes in direction of force. It now becomes con-



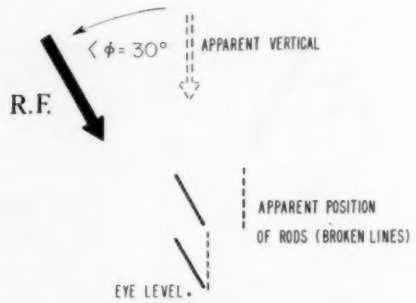
"POSITIVE" OCULOGRAVIC ILLUSION. BOTH RODS (SOLID LINES) ARE FIXED IN THE GRAVITATIONAL VERTICAL POSITION (RIGHT ANGLE TO FLOOR OF CENTRIFUGE). HEALTHY SUBJECT REPORTS (APPARENT) CHANGE IN POSITION OF RODS APPROXIMATELY AS SHOWN BY BROKEN LINES. HE ROTATES RODS COUNTERCLOCKWISE TO POSITION OF ARROW (BROKEN LINES) TO INDICATE THE "VERTICAL".

FIGURE 5

tinuous with the drive shaft of the motor which could be activated either by the subject or by the operator in the control room causing the rods to rotate either clockwise or counterclockwise. Selsyn repeater motors attached to the shaft activated a pointer in the control room, indicating the direction of the pendulum at all times. This could be compared with the actual direction of resultant force provided by another device.

If the rods are fixed in the gravitational vertical position and a healthy person observes them while undergoing a change in direction of resultant force, the rods appear to move to the position shown by the dotted lines in Figure 5. Actually, the rods bear a relation to resultant force as shown by the solid lines while the subject assumes that the positions are as shown by the dotted lines. If the subject is requested to rotate the rods to the vertical position, he causes them to move counterclockwise about 30 degrees. This form of the illusion, in which a stationary object appears to move, has been termed the positive form of the oculogravic illusion.

If the rods are now freed and allowed to assume the direction of resultant force, their actual position in relation to this force will



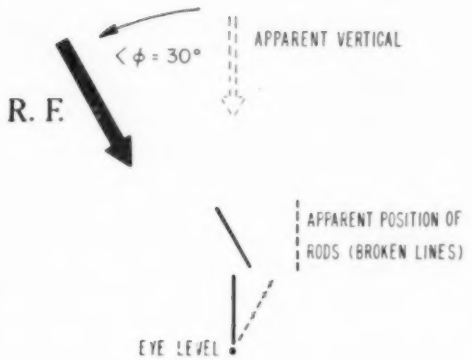
"NEGATIVE" OCULOGRAVIC ILLUSION. BOTH RODS (SOLID LINES) FREE TO ASSUME DIRECTION OF RESULTANT FORCE (R.F.) HEALTHY SUBJECT REPORTS POSITION OF RODS APPROXIMATELY AS SHOWN BY DOTTED LINES.

FIGURE 6

be as shown in Figure 6. In effect, they will have rotated counterclockwise 30 degrees. The subject now declares that they appear upright; the upper rod appears slightly farther to the right than the bottom rod because it is farther above eye level. The dotted lines in Figure 6 show the relationships which the subject believes to be the case. This has been termed the negative oculogravic illusion in which a rod, free to assume the change in direction of resultant force, appears to remain vertical.

The combination of positive and negative illusions is shown in Figure 7. The great advantage of using this combination is that one rod serves as a reference for the other, and even if the subject is uncertain as to the vertical, he is certain with regard to the relation of the two rods. This combination was always valuable and sometimes essential in the indoctrination of deaf subjects.

Healthy persons and subjects with a single functioning labyrinth when subjected to a change in direction of resultant force report the findings indicated in the upper half of Figure 8. Nine deaf subjects who either did not respond to massive irrigation of the external auditory canals or who showed just perceptible nystagmus fell into two groups: seven who did not see the illusions, and two who did. It was assumed that those who did not see the illusions had lost the function



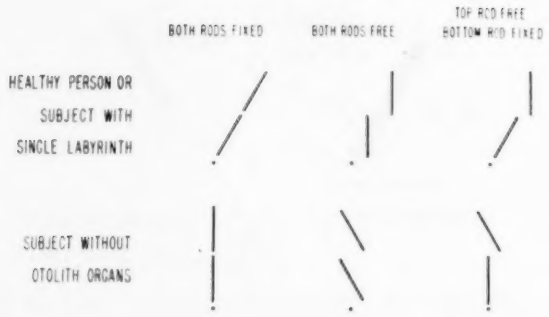
COMBINED POSITIVE (LOWER) AND NEGATIVE (UPPER) ILLUSIONS.
TOP ROD FREE; BOTTOM ROD FIXED.

FIGURE 7

of the otolith organs on both sides. Each of these seven perceived the positions of the rods as shown in the lower portion of Figure 8.

Experiments Utilizing a Collimated Star. Reference should be made to earlier reports from our laboratory for details concerning the experiments on the oculogravic illusion. Highly sophisticated healthy subjects were used. In all of the experiments the subject was exposed to a change in direction of resultant force while viewing a collimated star in the dark. This "star" consisted of a central spot with radiating lines placed at infinity by means of an optical system.[18] This visual target was under the control of both subject and experimenter. Either could rotate the star clockwise or counterclockwise, and a record was made of the axes of the star in relation to the gravitational vertical and the direction of resultant force. In this way it was possible to compare the subject's perception of the horizontal with the direction of accelerative force under a variety of conditions.

Threshold Measurements. These measurements were made in terms of the angle ø, i.e., the angle made by the vectors representing



A COMPARISON OF THE SUBJECTIVE REPORTS OF PERSONS VIEWING LUMINOUS RODS IN THE DARK WHILE EXPOSED TO A CHANGE IN RESULTANT FORCE (ANGLE $\phi = 30°$) RELATIVE TO THEMSELVES

FIGURE 8

gravitational force and resultant force. It was found that the mean threshold for three subjects in the sitting position was 1.5°; when lying on the right side it was 8.9°; when upside down it was unobtainable within a limit of 12°.[19] These findings accord with Quix' hypothesis, namely, that the otolith apparatus functions best with head upright and may fail to function with head down.[20]

Accuracy. The accuracy with which a subject was able to estimate the change in direction of resultant force varied with the circumstances. Under ideal experimental conditions and if the angle ø was not greater than 45°, the subject's estimation was not only accurate within a few degrees but was also consistent. Individual variations were observed, some consistently overestimating and others underestimating the angle, the former predominating.

Adaptation. It was found that when subjects were exposed to a change in direction of resultant force for fifteen minutes, there was no evidence of adaptation.[21] In other words, their estimates of the horizontal showed no significant change, and there was no significant change in the accuracy of their settings. It should be pointed out

that adaptation has been observed when subjects are tilted with respect to gravity.[13,22] However, the situations are not strictly comparable. The greater magnitude of resultant force may be a factor and the lag phenomenon must be taken into account.

The Lag Phenomenon. When subjects were exposed to a sudden change in direction of resultant force, there was a relatively long delay before the apparent movement (rotation of the star) ceased and the target had completed its full excursion. If this lag is regarded as a temporary error in making the adjustment, this undercorrection is not great in magnitude, but the duration is often longer than one minute.[23] If this lag is explicable on the basis of peripheral end organ, it suggests that there is overdamping in terms of the movement of the sensory hairs in a viscous matrix.

The Genesis of the Illusion. Explanation of this illusion cannot be made adequately on the basis of eye movements.[5] It must be sought in an influence of sensory elements which orient us to resultant force on visual space perception. There are strong reasons for believing that the genesis lies in the otolith organs. This illusion may be regarded as a tendency to bring visual and non-visual space-perception cues into uniformity. It is masked in ordinary life but is disclosed readily during flight in aircraft and under experimental conditions.

THE SIGNIFICANCE OF THE OTOLITH ORGANS IN MAN

No attempt will be made here to give a full account of the importance of the otolith organs which has been the subject matter of a number of excellent reviews.[24-29] However, those aspects of this problem which have come within our experience will be briefly mentioned. The first is concerned with disturbances in function due to disease, the second with loss of function, and the third with normal function.

DIFFERENTIAL SYMPTOMATOLOGY IN PATIENTS WITH MIDDLE EAR DISEASE

During the course of an investigation on the residual effects of unilateral labyrinthectomy in five adult women, the opportunity arose to compare, in the same person, the abnormal symptomatology with the symptoms induced by selective stimulation of the semicircular canals and otolith organs. When these individuals were subjected under controlled conditions to angular acceleration in a modified Link Trainer,

DIFFERENTIAL SYMPTOMATOLOGY ASSOCIATED WITH DISEASE AND DISORDER OF MIDDLE EAR			
SYMPTOM	COCHLEA	S. C. CANALS	OTOLITH ORGANS
DEAFNESS	+		
TINNITIS	+		
SUBJECTIVE VERTIGO (ROTATION)		+	
VISUAL VERTIGO		+	
SUBJECTIVE ILLUSION BODILY TILT			+
VISUAL ILLUSION OBJECTS TILTED			+

Fig. 9

they experienced sensations of rotation and visual vertigo (the oculogyral illusion) in nearly all respects similar to those experienced by healthy persons.[30] When exposed to a change in direction of resultant force on the human centrifuge, they perceived the bodily tilt and the oculogravic illusion.[31] When their abnormal symptomatology was reviewed in the light of their laboratory experiences, certain similarities were recognized.[6] The spontaneous symptoms were referable mainly to the semicircular canals in two of the women, to both semicircular canals and otolith organs in two, and to the otolith organs in one. The most common characteristic differential symptoms are shown in Figure 9. These must be sought oftimes among a great number of other complaints.

Absence of Otolith Function. Nearly 300 deaf persons were subjected to screening tests in an effort to obtain selected subjects. Some of the findings are summarized in Figure 10 for seven persons

A COMPARISON OF FINDINGS IN DEAF SUBJECTS WITH BILATERAL DEFECTS OF THE NON-ACOUSTIC LABYRINTH

SUBJECT	SEX	AGE	RESIDUAL FUNCTION NON-AC LAB	HISTORY DIZZINESS MOTION-S	PSYCHO-MOTOR HANDICAPS				DURATION OF STANDS (SEC); EYES CLOSED		
					WHOLE BODY		BODILY COMPONENTS				
					VISION	VIS REDUCED	VISION	VIS REDUCED	BOTH FEET †	LEFT FOOT ‡	RIGHT FOOT ‡
H S.	F	51	NONE	NONE	NIL	MOD.	NIL	NIL	60;60; 60 60	2; 2; 2 3	2; 2; 1 1
G B.	M	32	NONE	NONE	NIL	MOD	NIL	NIL	60	2	12
R F	F	26	NONE	NONE	NIL	SL-MOD	NIL	NIL	60	2	2
P T*	F	31	NONE	NONE	NIL	SL-MOD	NIL	NIL	60,60,60	2 , 3; 2	2, 2, 1
E S*	M	45	NONE	NONE	NIL	MOD.	NIL	NIL	60	5	4
P H	F	37	NONE	NONE	NIL	MARKED	NIL	NIL	41;60, 60 60, 60	1 ; 2; 2 3 ; 4	1; 3; 2 4; 5
B B	M	51	NONE	NONE	NIL	MOD	NIL	NIL	60, 60	2 ; 2	2; 2
B D	M	17	OTOLITHS	NONE	NIL	SLIGHT	NIL	NIL	60, 60, 60 60, 60	4 ; 14; 16 30	2; 9,23 30
R G*	M	41	OTOLITHS	NONE	NIL	SL-MOD	NIL	NIL	60, 60, 60 60, 60	3 , 8; 6 6 ; 9	4; 4; 5 4; 6

* MINIMAL FUNCTION S C

† 60 SEC CUT-OFF

‡ 30 SEC CUT-OFF; ALL VALUES LESS THAN 30 REPRESENT MEAN OF 3 TRIES

‡ SERIAL FIGURES REPRESENT TRIALS ON DIFFERENT SUCCESSIVE OCCASIONS

Fig. 10

who, for all practical purposes, had lost all functions of the inner ear and for two subjects who had lost all functions save that of the otolith organs. Our studies are far from complete even on these nine, but a few preliminary remarks may be in order. We were particularly interested in discovering any differences between the two groups.

Careful inquiry was made regarding any history of dizziness or motion sickness. No symptoms were elicited. More specifically, a listing of situations was presented in which motion sickness is prone to occur. Insofar as these were encountered, they were not associated with any feelings suggesting motion sickness; deaf persons who have not lost the function of the semicircular canals, however, may become motion sick. We were particularly interested in the fact that the two subjects who had lost all function of the inner ear save that of the otoliths gave no history of motion sickness. We hope to increase the number of subjects in this group and to expose them to accelerations designed to stimulate the otolith apparatus and to situations where motion sickness is likely to occur. Our limited findings suggest

but do not prove that the semicircular canals and not the otolith organs are the chief labyrinthine organ concerned with motion sickness.

Inquiry was also made in regard to any handicaps in orientation and in carrying out co-ordinated movements. We relied partly on the subject's estimate of these abilities as compared with those of healthy persons and partly on our observation of the accuracy with which various co-ordinated movements and orientation tests were carried out. It was concluded that all nine were handicapped with regard to whole body orientation where visual cues were lacking but that there was no handicap regarding movements and orientation of component parts of the body.

Like many other investigators, we found that standing on one foot with eyes closed was a difficult task for the subjects to perform. The only subject who could learn to stand for thirty seconds had not lost the function of the otolith organs. The fact that he was young and athletically inclined was in his favor. It hardly need be pointed out that many healthy persons find it difficult to stand on one foot with eyes closed, a fact which limits the utility of this simple test.

Our experience thus far serves mainly to emphasize the difficulties involved in this approach. The selection of subjects is a considerable task, but eventually it should be possible to have a sizeable group with function of the inner ear limited to the otolith organs or, possibly, to the semicircular canals. However, this still leaves the difficult problems of a quantitative estimation of this function, the evaluation of deficiencies due to loss of hearing, and the extent to which compensatory learning and adjustment have taken place.

THE FUNCTION OF THE OTOLITH APPARATUS IN HEALTHY PERSONS

Our observations in this regard may be summarized briefly as follows:

The otolith apparatus subserves the function of orientation to gravity and to forces of acceleration equatable with gravitational force.

Orientation to gravity is equivalent to orientation to the center of the earth. When man is upright, the otoliths are a precise indicator of whole body orientation to the earth; when man is on his side the indication is crude; and when inverted it is very poor or nil. Under static conditions there is little or no adaptation. Under dynamic con-

ditions, i.e., change in position relative to the direction of gravity, the otoliths signal the initial and greater proportion of the change fairly rapidly but lag behind the event in signalling the final smaller proportion of the change. This lag is greater in movements which displace the sensory elements from their natural position when the head is upright than in movements in which these elements are returned to this position. There is little or no tendency toward overshoot. The perception of bodily alignment with gravitational force is a resultant of afferent stimuli from many sources and the contribution of the otolith apparatus ordinarily tends to be masked. The relative importance of the otoliths becomes greater under conditions in which other gravitational cues are reduced as exemplified by immersion in water and absence of vision. A unique characteristic of the otoliths is their influence on visual space perception. This is declared by a tendency for visual space perception to conform with nonvisual space perception.

Under all conditions where man is exposed to accelerations which are equatable with gravitational acceleration, the otoliths respond to the resultant force. Here it is necessary to distinguish between forces greater and forces smaller than gravity and to take into account both the direction and magnitude of such forces. Under ordinary living conditions these linear accelerative forces are small. Although these forces provide a stimulus which is often suprathreshold its influence on our behavior is negligible. It is only when man's natural powers of locomotion are extended by mechanical means that he is subjected to forces which influence his behavior to a significant degree. Thus, a tolerable increase of inertial force, in which the direction is concordant with the longitudinal body axis, and the sense of the force from head to foot, the otoliths tend not only to orient the person to his immediate environment but also tend to bring his visual perception of the earth's axes into conformity with the axes of his immediate environment. When a person is subjected to an increase in resultant force, the direction of which is discordant with respect to his longitudinal body axis, the individual is not only aware of a bodily reorientation to this force but is aware of a characteristic feeling which may have its origin in the otolith organs. Moreover, in this circumstance there is a compelling tendency to make visual space perception conform with egocentric space perception based on nonvisual bodily orientation; with moderate increases of resultant force this conformity may be fairly precise but, at a critical level, there is not only over-

compensation but also there may be an illusion involving relative movement.

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XXXIX

THE ANALOGY BETWEEN FLUID MOTION WITHIN THE COCHLEA AND FORMATION OF SURF ON SLOPING BEACHES AND ITS SIGNIFICANCE FOR THE MECHANISM OF COCHLEAR STIMULATION

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Probably the most intricate of the mechanical phenomena arising within the ear in response to acoustic stimulation concerns the transfer of vibratory energy from the footplate of the stapes through the cochlear fluids toward the organ of Corti. Among the older theories, the so-called Place Theories were favored by most of the evidence collected in various fields: clinically, histologically, as well as experimentally. Yet these theories, notably among them the "resonance theory," did not account for the exact mode of energy transfer in such a way as to hold up against criticism. This situation began to alter with the advent of the modern "hydrodynamical theories" which are based chiefly upon the experimental evidence presented by von Békésy. To quote Fletcher: "Any theory must be consistent with these data of Békésy . . ."

After Békésy had published his findings, several mathematical analyses were presented. A critical evaluation of these papers would be far beyond the scope of the present writing. Therefore, a brief attempt of classification as to their general approach may suffice.

Ranke,[7,8] based upon earlier attempts of Frank, treated the problem as one related to that of surface waves.

Zwislocki,[18] basically also a proponent of the surface-wave analogy, held damping as the decisive factor for the establishment of the cochlear phenomenon.

Peterson and Bogert[5] and Bogert[1] approached the problem from its likeness to certain phenomena in electrical transmission-like net-

works and also emphasized the role of energy dissipation due to damping.

Fletcher, who in earlier years had started to develop his "space-time pattern" theory, gave a recent summary[2] which took account of Békésy's published data as to material constants, dimensions, etc.

The basic requirement to the understanding of these papers is a considerable knowledge of physics and mathematics. Consequently, they are but of little help to the non-technical reader who seeks information about the mechanism underlying the cochlear phenomenon.

When one is trying to introduce students to a very intricate problem, one may resort to a time-honored method in teaching by demonstrating an analogy with a more familiar and a more tangible phenomenon. Such an analogy must not necessarily be correct to the last detail in order to constitute a good teaching aid.

To this writer the analogy between cochlear fluid motion and surf on sloping beaches has served for some time as a teaching aid, quite satisfactory in the sense just outlined. Incidentally, Ranke has also made mention of this analogy in his writings; but apparently he was misinformed about one important detail, namely the location in relation to the shore at which long or short waves form surf, for he soon disregarded the analogy as being not quite appropriate. The present author does not propose to be an authority in the field of hydrodynamics, but over a span of many years he has collected some empirical knowledge concerning the behavior of surface waves in many different waters. This, in his opinion, may enable him to discuss the problem intelligently and to conduct a series of experiments, both in surf and in cochlear models.

COCHLEAR DYNAMICS

First, a brief review will be made of the observations by von Békésy pertaining to the problem of cochlear dynamics. The first three graphs taken from Békésy's publications contain some essential aspects of his findings. On vibratory stimulation of the stapes footplate, a wave-like displacement is origination along the cochlear duct. The entire cochlear duct, from Reissner's to the basilar membrane and all the structures contained therein, moves as a unit in the execution of this displacement. Therefore, the problem is greatly simplified by considering the cochlear duct as a simple, two-dimensional partition between the two perilymphatic scalae: "the cochlear parti-

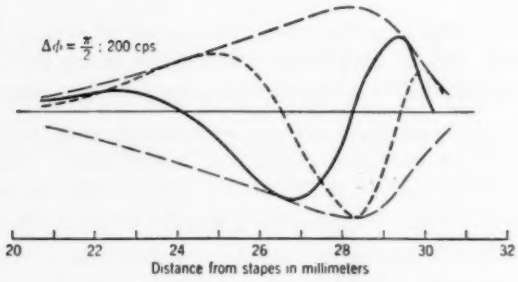

Fig. 1.—Traveling wave along the cochlear partition for a 200 cycle tone. The solid line indicates the deformation pattern at a given instant. The line with the short dashes shows the same traveling wave ¼ of a period later. The envelope shows the maximum displacement at each point. (After Békésy, 1947).

tion." The waves are synchroneous with the frequency of stimulation and travel continuously along the cochlear partition toward the helicotrema. This phenomenon is known as the "traveling bulge." Figure 1 shows this bulge at two instances, apart from each other for 90° of phase, and surrounded by their common envelope, i.e., a line which "envelopes" the motion at all times. The pattern of this envelope indicates that the traveling bulge, after building up toward and passing through a maximum, decreases rather rapidly to an almost imperceptible fine ripple (the latter fact is not shown in the graph). Throughout the variation of amplitude, the distance from wavecrest to wavecrest becomes progressively shorter as the bulge moves along its path. Since the stimulating frequency does not alter, the lessening of the wave length implies that the wave velocity is slowed down proportionally. This latter fact is derived from consideration of the well known relation:

$$\text{frequency} \times \text{wavelength} = \text{wave velocity}.$$

Figure 2a indicates that the location at which the amplitude maximum of the traveling bulge is formed moves closer toward the windows and its envelope becomes narrower, when the frequency is raised, and vice versa. Figure 2b depicts the phase vs. distance relationship. The angle of phase with respect to that of the stapes changes over the entire course of the bulge in a cumulative (although not

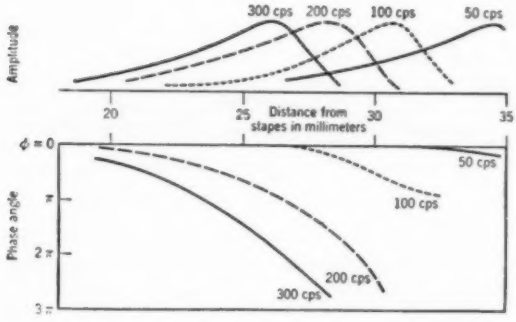

Fig. 2.—Amplitude and phase angle of the cochlear partition at various distances from the stapes. For frequencies above 100 cps the difference in phase may exceed one π. At 50 cps the membrane vibrates in phase. (After Békésy, 1947).

entirely linear) fashion, especially so after the location of the maximum has been passed. This finding is one of the strongest arguments for the fact that one is actually dealing with a traveling event instead of a case of a localized resonant phenomenon.

Figure 3, finally, shows the traveling bulge in response to a single impulse. In this case, the wave motion is not restricted to a limited area, but a single wavecrest is seen traveling all the way up to the helicotrema. Similar to the sustained event, the velocity of propagation decreases steadily with distance from the windows. Indicated also in this graph is the occurrence of a pair of symmetrical eddies, one in each of the perilymphatic scalae. On sustained stimulation, these eddies establish themselves about at the location of the maximal amplitude and may be used for easy identification of the latter.

The logical link between the cochlear phenomenon and surface waves as observed in surf is given by some others of Békésy's findings:

1) The phenomenon of the traveling bulge was found to occur in an essentially similar manner in coiled (mammalian) cochleae as well as in non-coiled models thereof, which greatly simplifies model experimentation. It may be remembered that the equivalent structure in birds and reptiles, the lagena, is also straight and not coiled.

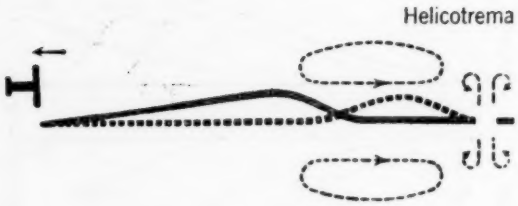

Fig. 3.—A sudden displacement of the stapes gives rise to a traveling bulge along the cochlear partition. The dashed line indicates the position of the bulge at a later time. The bulge pushes fluid ahead along the surface of the partition. The bulge disappears at the helicotrema and the fluid flows back to its original position, creating eddies (dotted ellipses). (After Békésy, 1933).

2) When the mechanical properties of the cochlear partition were investigated, its mass was found to be relatively unimportant for the formation of traveling bulges, a fact which is another justification for the substitution of the three-dimensional cochlear duct by the two-dimensional cochlear partition. The decisive factor for the traveling bulge is the stiffness of the cochlear partition. It was found to vary systematically with distance along the cochlear partition, being approximately two hundred times higher at the windows than at the apical end.

3) The traveling bulge was found to be a remarkably stable event and not notably affected by such changes as draining of the fluid from the tympanic scala.

These three findings link the cochlear events, which are essentially interface phenomena, to waves traveling upon the surface of fluids. The elastic factor responsible for surface waves is actually a complex one, being composed of surface tension, a property of all free fluid surfaces, and gravity, a (downward) restoring force and by this latter definition elastic in character. Surface tension is the dominant factor in very small waves (so-called capillary waves; wavelength smaller than 1.7 cm), whereas gravity becomes the decisive factor for waves larger than this limit.

SURF

Surface waves and surf may be observed on any large body of water and on almost any beach. However, their demonstration is greatly facilitated in a so-called flume, an oblong water tank with glass walls, in which any desired form of wave motion may be simulated. A series of demonstrations and simple experiments was conducted in a flume at the Iowa Institute for Hydraulic Research and photographically recorded with the aid of motion picture films, including slow motion pictures.

The most common form of surface waves are wind waves, one of their characteristics being that the driving force (the wind) is effective over a large surface area. Within the cochlea, the driving force (the action of the stapes) produces another type of waves, known as displacement waves. In the flume, displacement waves may be originated by a wave generator, which consists of a motor-driven paddle producing effective strokes in the forward direction only. The frequency and amplitude of this generator can be controlled within certain limits.

Surface waves obey most of the general laws of wave motion with a few noted exceptions. Waves propagating within a given medium, e.g., sound waves in air, are known to maintain their wavelength and wave velocity no matter how far they may travel. In contrast, surface waves do not maintain their wavelength and their velocity. This can be demonstrated even within the confinements of the flume. To this end, a series of three or four crests is suddenly originated. Adjacent to the wave generator, waves appear short and relatively high, whereas after some distance of travel, at the opposite end of the flume, they have gained wavelength but have lost amplitude. This apparent exchange between wavelength and amplitude is important for the present problem. We shall return to it later. Although it is not as easily observed, wave velocity increases in direct proportion to the wavelength because of the relationship between frequency, wavelength, and wave velocity outlined above. This fact is of practical consequences: In open water, "older" waves have always larger wavelength and travel faster than "young" waves.

Since fluids are incompressible for all practical purposes, motion of surface waves cannot be limited to the very surface, that is, particle motion extends quite a way down from the surface. In other forms of waves, particle motion may be transversal, like that of light accord-

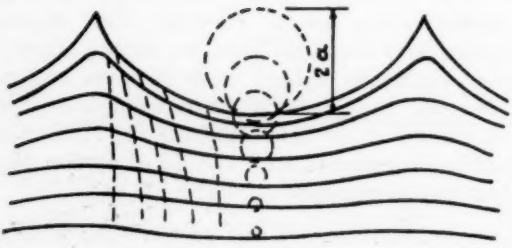

Fig. 4.—Surface waves in deep water (schematic) showing the circular variety of trochoidal particle motion. Amplitude diminishes gradually with depth. Compare with Figure 8. (After Miniken).

ing to its wave theory, or longitudinal, like that of sound waves in air. In surface waves in deep water particles move around a circular path, which is known as a "trochoidal" mode (Fig. 4). The amplitude of this motion diminishes gradually with depth until finally it becomes immeasurably small. For example, during a moderate gale in the open Atlantic, wave motion was experienced as a gentle rocking sensation to depth of about 25 fathoms, equal to 150 feet, until with further increase in depth it faded out completely (personal experience).

When surface waves hit upon a sloping obstacle, surf is formed. For comparison of the behavior of waves in surf and that of unhindered waves, the flume was divided in two parallel channels by means of a glass plate; a slope was placed on only one side of the partition (Fig. 5). In comparison with the free channel, the following points were noted:

1) A gradual accumulating phase lag, i.e., wave velocity and wavelength become progressively smaller. Furthermore the crests become skewed, with the steeper slope pointing toward the obstacle (Figs. 5 and 6). In maritime parlance, this event is known as "crowding" of waves.

2) At the same time, the transversal amplitude of the waves is built up (Fig. 6).

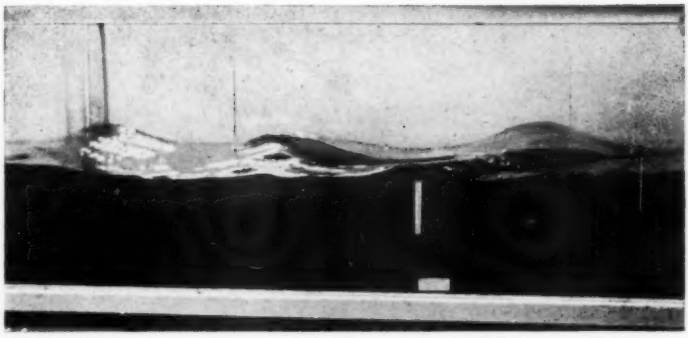

Fig. 5.—Section of the flume divided in two parallel channels. The outer channel is free; the slope is in the inner one. Wave frequency: 80 cpm. Note the phase lag gradually accumulating over the three crests shown. The amplitude maximum is not seen, because the 2nd crest has just passed it and has already started breaking an instant before the picture was taken.

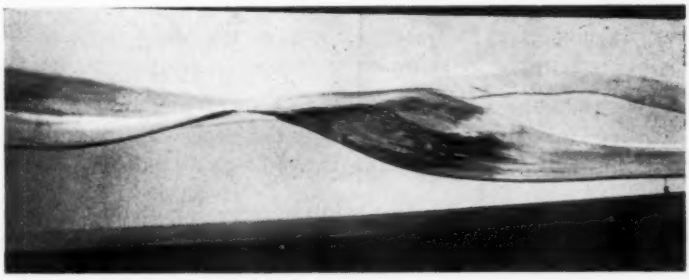

Fig. 6.—Close-up of a wave crest approaching the slope. Note phase lag and slight elevation of amplitude with respect to the outer (free) channel. Points adjacent to the glass partition must be compared. The distal slope of the crest is already steeper than the proximal one (skewness) and shows some irregularities upon its surface which are indicative of imminent breaking. Wave frequency: 40 cpm.

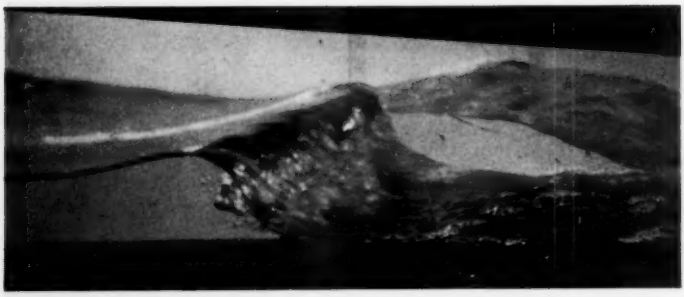

Fig. 7.—Same wave as in Figure 6 an instant later. The amplitude maximum has been reached, the skewness is very pronounced, and breaking has just begun. The irregular surface stretching distally to the crest is part of the backwash of the predecessor (wave of translation).

3) After reaching a maximal amplitude, the waves begin to break and thereafter lose their amplitude rather rapidly (Figs. 5 and 7).

4) The point of maximal amplitude is remarkably stable as long as frequency and amplitude of the driving force are kept constant. If, however, the frequency is increased, while the amplitude is kept constant, the breaking starts earlier, i.e., farther off-shore.

5) The terminal action of surf consists of an alternating longitudinal lapping of water up and down the slope which was descriptively named by Lord Russel the "wave of translation."

A brief analysis will be made in the following of the events just outlined without resorting to their exact but rather complex mathematical formulations.

On free distribution of waves, wavelength and wave velocity were seen to increase, while the amplitude decreased. Against the slope, the reversed was found to tak place. These two findings indicate that the two factors, wavelength and amplitude, are reciprocally related to each other and suggest that their product represents the total energy contained in a given train of waves. The exchange of wavelength and amplitude may best be illustrated by the following example: Submarine earthquakes often originate very steep wave

fronts of tremendous power. From their place of origin such "tidal" waves travel over vast stretches of the ocean, constantly gaining velocity (and wavelength) but becoming quite low in amplitude and inconspicuous. When they finally reach a distant shore, they build up amplitude suddenly and seemingly out of nowhere crash upon the shore with unexpected force.

The property of freely propagating waves to gain wavelength while losing amplitude may be interpreted as a tendency toward restoration of the resting state of the surface. Surface waves being a disturbance of this resting state are then basically unstable. For reason of this instability, surface waves cannot grow indefinitely, but are limited to a certain wavelength to height (i.e., 2x amplitude) ratio which for water happens to be 7:1. Whenever this critical value is exceeded, waves start to break, thereby losing their amplitude again. The breaking of waves in surf is further facilitated by the aforementioned skewness of the waves.

Basically, the propagation of ordinary surface waves, i.e., that of non-breaking waves, represents a laminary motion, whereas breaking introduces eddying. From the classical investigations of Poiseuille and of Reynolds it is known that the resistance against a moving body of fluid (which determines the energy dissipation) raises to the square of whatever value it may have had, as soon as laminary motion converts into eddying motion. This is one of the reasons for the decrement of amplitude in surf as soon as the waves start breaking. Another, perhaps more important reason will be discussed later on.

The series of related events: crowding, amplitude build-up, and breaking of waves, are not only seen on sloping beaches. They occur whenever surface waves enter into shallow water and are slowed down. However, this "shallow-water" opposition causes waves to break in an entirely random manner so that one cannot speak of surf at all. The telltale "choppiness" of waves, i.e., their newly acquired steepness, indicates to the experienced sailor when his ship is approaching a shoal.

In shallow water particle motion is no longer circular (Fig. 4) but becomes elliptical instead (Fig. 8). With distance from the surface the vertical (short) diameter of these ellipses decreases so that near the bottom of the flume the motion becomes purely longitudinal. In surf, this latter motion is gradually brought to the surface by the emergence of the slope, thus forming the terminal action of surf: the wave of translation.

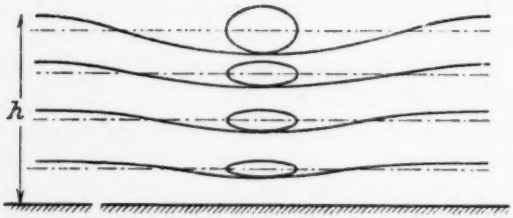

Fig. 8.—Surface waves in shallow water (schematic) showing the elliptical variety of trochoidal particle motion. The vertical (small) diameter of the ellipses diminishes with depth. Compare with Figure 4. (After Richardson).

If one wishes to investigate the difference between the mere "shallow-water" opposition and the more complex formation of surf, one may study the build-up period of surf subsequent to the arrival of the first crests of a steep wave front upon the slope in the flume. With the aid of slow motion pictures the following observations are made: The first crest approaching the slope is crowded, shows some amplitude build-up (although less than the sustained event), and finally starts breaking. It runs unusually high upon the slope, continually breaking and losing amplitude. When the water pushed up by the first crest eventually recedes, it is met by the approaching second crest cutting under it and preventing the latter from reaching quite as high upon the slope as did the first crest. This interference between each wave and the rebound of its predecessor continues over the following cycles with the effect that the amplitude maximum becomes gradually higher and the decrement more pronounced, until a stable condition is reached approximately with the sixth crest (Fig. 9).

This description leaves no doubt that the build-up of surf resembles that of a cyclic event, for instance, that of a resonanting system. Furthermore, reflection seems to play a major role in this build-up.

Reflection from a slope into the direction of the incident beam would be quite impossible in waves propagating within a medium, e.g., in the case of sound waves in air. However, as is implied by their very name, the energy distribution of surface waves is limited

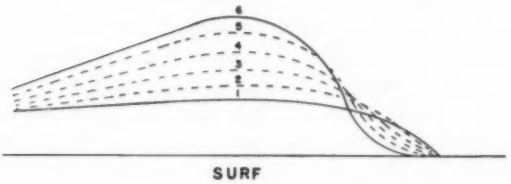

Fig. 9.—Envelope over the first six crests of surf originated by a steep wave front. If motion is continued, the envelope does not change further after the sixth crest has passed. Compare with Figure 10. (Schematic reconstruction from slow motion pictures (64 frames/sec.) taken in the flume).

to the surface layer making this form of reflection feasible. If reflection is recognized as one of the causes of surf, the question may be raised whether or not standing waves may occur. Standing waves are a common sight in narrow harbor basins which are surrounded by steep piers. However, as it was shown above, the incident and the reflected waves of surf are not alike, which is one of the prerequisites for the origination of standing waves; the first one being trochoidal and the latter one translatory in nature. This dissimilarity leads the rebound of each wave to cut under the inbound motion of its successor. These two movements, tangentially to each other, occur in opposing directions producing what is known technically as a "shearing effect." Shearing greatly enhances the crowding and subsequent breaking of surface waves, as is easily observed in so-called "roosts," in which wind waves run against opposing tidal currents.

If fine particulate matter is suspended in the water of the flume, it can be demonstrated that the rebound motion actually extends far back along the bottom under the incoming waves. This "drag" or "undertow" effect is familiar to all surf-bathers. Eventually, at some distance from the shore, the drag movement becomes very broad and diffuse and turning upward gradually joins the inbound motion forming a large, slowly revolving eddy. The drag running under and in opposition to the inbound waves exerts an additional slowing-down effect upon these waves. This results in further crowding and building up of the amplitude maximum, and, by augmenting the breaking of the waves, in a steeper decrement beyond the maximum.

Finally, a word about the effect of wave frequency upon the location at which the amplitude maximum is formed. Ranke's misin-

formation in this respect, which was mentioned above, is apparently based upon a widely popular misinterpretation of the following observation: If wind waves run upon coastal flats which on many coasts extends for miles off-shore, they may form a primary surf at the boundary of these flats. Thereafter, the wind whips up new and shorter waves which upon reaching the shore-line proper may form a secondary (smaller) surf. Ergo: long waves form their surf farther off-shore than short ones. The fallacy of this conclusion becomes obvious when one observes such shores being hit by severe storms with real long waves. In that case, surf is formed within the (usually) protected in-shore area.

The known facts about surf and cochlear phenomena can be summarized in the following statements:

1) The two events are similar in that both concern effects upon progressing surface or interface waves. These waves are slowed down and subsequently crowded, thereby building up amplitude. After reaching a maximum, a steep decrement of amplitude takes place.

2) The location of the maximal amplitude depends upon the frequency of stimulation in such a way that with lowering of the frequency the location of the maximum moves in a distal direction. Simultaneously, the envelope over the entire event becomes broader.

3) A detailed analysis of surf, as the more tangible of the two phenomena, suggests that surf results from two causes: "shallow-water" opposition and reflection.

a) The "shallow-water" opposition represents an element of friction, i.e., damping, and is responsible for the initial slowdown of wave motion which leads to crowding, some build-up of amplitude, and eventually to breaking of waves and a subsequent decrement of amplitude.

b) Reflection, i.e., a phase inversion of the terminal (longitudinal) motion of each wave, causes a shearing interaction between the inbound and rebound motion. This shearing effect represents an additional dissipative force. It greatly enhances the slowdown of the incoming waves and its sequelae: crowding and amplitude build-up, breaking and the ultimate steep decrement of amplitude. Inbound and rebound motions are continuous with each other forming a large, slowly revolving eddy, inbound along the surface and rebound along the bottom of the slope.

SIGNIFICANCE OF THE ANALOGY FOR COCHLEAR DYNAMICS

The question now arises how far this detailed description of surf may prove helpful toward a further analysis of the cochlear events. It is folly to assume that an analogy fitting several aspects of two events must necessarily make the two analogous in all respects. But there is some evidence making an extension of the analogy quite probable. For instance, the bulge originated by an impulse travels all the way to the cochlear apex (Fig. 3), as does the first crest of surf.

Of course, nothing is known so far about the mode of transition from this initial event to sustained cochlear vibrations.

To answer these questions, experiments were conducted on cochlear models built similar to those used by von Békésy. These experiments will not be discussed in detail at present, but will be described in a future paper.[12]

In surf, the existence of reflection was best demonstrated by showing the gradual increase of its effects during the build-up subsequent to the arrival of a steep wave front at the slope (Fig. 9). Therefore, the onset of sustained vibrations within the cochlear model in response to various stimulation frequencies was recorded with the aid of a high-speed motion picture camera capable of film speeds up to 3000 frames/second. Subsequent projection at 16 frames/second slows even fast events down to a comfortable viewing speed. For instance, one cycle of a 100 cps vibration lasts for almost two seconds on the projection screen. The frequency response of the model used in these experiments was from below 10 cps up to approximately 500 cps; frequencies higher than 100 cps being especially suited for the purpose of the present study because there was an appreciable stretch of the membrane distal to the amplitude maximum which showed no motion on sustained vibrations. As a general analysis of these high-speed motion pictures the envelopes over the first three crests are given in Figure 10. The general pattern is the same as that in surf (Fig. 9), although in the cochlea the period of transition is completed in a lesser number of cycles and the amplitude maximum of the established event seems somewhat more peaked. For higher frequencies, the backing-off of the envelope from the distal end was quite substantial. For instance, for 200 cps, under 16× microscopic magnification and along a membrane of 50 mm, the following numerical values were obtained: envelope of the first crest: 50 mm, second crest: 28 mm, from third crest on: 22 mm, with the maximum occur-

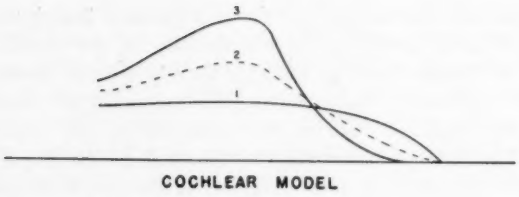

Fig. 10.—Envelopes over the first three crests originated within a cochlear model upon sudden onset of stimulation (frequency: 100 cps). After the third crest, the envelope does not change further. Compare with Figure 9. (Schematic reconstruction from high-speed motion pictures (3000 frames/sec.))

ring at 20 mm. Incidentally, at these higher frequencies, the first crest took quite a while to make its way to the apical end of the membrane, a fact which was less obvious for lower frequencies. In terms of successive crests, the first crest did not reach the distal end, until the sixth crest had appeared at the maximum. This represents a phase difference of 12 π and may be compared with the results presented in Figure 2.

Since the damping within the model was made to simulate that of the actual cochlea, the latter being much higher than that within the flume, this was thought to be responsible for the quantitative difference between the patterns of Figures 9 and 10. To test this thesis, the damping within the model was lessened which led to build-up patterns more closely resembling that of surf (Fig. 9) than that given in Figure 10. The resulting broadening of the envelope over the established pattern may be illustrated by the following figures, pertinent to a stimulation frequency of 100 cps. When the damping was high, the distal end of the envelope was found at 35 mm (under 16$\times$ magnification). When the damping was decreased to approximately one-third, the envelope extended all the way to the apical end of the membrane, viz., to and possibly beyond 50 mm. It must be noted in this connection that the alteration of damping affects only the broadness of the envelope, but in no way the location of the maximum.

To find out about the possibility of a shearing motion within the cochlea, the movement of particles within the cochlear fluids was

studied. Figure 11 shows a schematic outline of particle motion within the vestibular scala throughout Békésy's eddy. Superimposed upon the general course of the eddy are the pathways of individual particles in the four main positions. (Actually, these particles and their pathways revolve slowly along the eddy's course.) The particle motion is trochoidal, of the elliptical (shallow-water) variety. Pertinent to our present problem is the finding that the particles in the inbound and in the rebound portions of the eddy are in direct phase opposition to each other because of a phase lag gradually accumulating throughout the eddy. Since the amplitude of particle motion does not diminish toward the center of the eddy (although it does decrease rapidly in an outward direction) the particle motion in opposing directions along the membrane and along the outer wall represents a shearing motion. In the same manner as in surf, this shearing effect must be held responsible for the fact that under no circumstances, neither in models nor in actual specimens, standing waves have ever been observed.

After one has described the similarities between two analogous events, it may be worthwhile to point out in which respect the two events are dissimilar. The difference in damping was already mentioned. Another one lies in the following. Within the cochlea, a gradient of stiffness was described, decreasing along the cochlear partition from the windows toward the apex. This is certainly not so in surf, where the elastic factor was said to be made up by gravity and by surface tension, both of which do not change with distance. However, if one thinks the water upon a slope divided in vertical slices of uniform width and running parallel to the shore line, the amount of water, the mass, contained in each slice becomes gradually less as one approaches the water's edge. This then represents a (decreasing) mass gradient. In contradistinction the width of the perilymphatic scalae varies but insignificantly over most of the distance of the cochlea, according to measurements made by Keith. This indicates that there is no systematic gradient of mass within the cochlea. Yet the behavior of both systems in response to vibratory stimulation is very similar, as was demonstrated in the present paper.

Peterson and Bogert had likened the cochlear phenomenon to events observed in electrical transmission-line networks. Instead of the mechanical elements of mass, stiffness, and friction, such networks are made up by their electrical equivalents: inductance, capacitance,

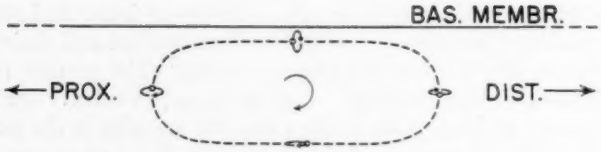

Fig. 11.—Particle motion (schematic) in the vestibular scala of a cochlear model throughout Békésy's eddy (dotted line). Direction of eddy and particle revolution as indicated. The instantaneous phase of particles in each of the four main positions is given by the small open circles and indicates a phase lag gradually accumulating throughout the eddy to a total of 360°. (After (12)).

and resistance. An example of such a transmission line is an ordinary telephone or telegraph cable.

Again, this is not the place to go into details of the theory on electrical networks, except for the following points. Traveling waves are found also in certain electrical transmission lines. The occurrence of localized amplitude maxima depends upon reflection from the distal end.[16] Networks showing these effects are often referred to as "tapered" networks; for the capacitance within the network grows with distance, i.e., they display a (positive) gradient of capacitance. (Because of the reciprocal relation between stiffness and capacitance, this is equivalent to a negative gradient of stiffness of a mechanical system). Although networks with a capacitative gradient are more common, essentially the same effects take place in other networks which possess a (negative) gradient of inductance.[13] The ratio of inductance to capacitance in each link of such networks represents the terminal impedance of the link (or to be exact: only its reactive portion). It is the (terminal) impedance which apparently must be "tapered" throughout the network in order to produce a "traveling-bulge" phenomenon. The inference of this last finding to the analogy between surf and the cochlear event is obvious: Both represent special cases of a general (mechanical) phenomenon.

SUMMARY

The analogy between cochlear fluid motion and surf on sloping beaches may be useful as a teaching aid. In addition, a detailed analy-

sis of surf, as the more accessible of the two phenomena, proved helpful to the interpretation of the mechanism underlying the cochlear phenomenon. It was shown that the eddy, originally described by von Békésy, is actually the outcome of reflection. Reflection in turn causes a shearing interaction between the inbound and rebound portions of the eddy. In conjunction with the energy dissipation due to damping, it is this shearing interaction which aids in shaping the characteristic pattern of the traveling bulge within the cochlea.

NOTE: A detailed summarizing account of the analogy was given at the end of the preceding chapter and need not be repeated here.

UNIVERSITY HOSPITALS

A sound motion picture (16 mm color) has been produced by the Motion Picture Production, State University of Iowa, under the title: "Analogy between Cochlear Fluid Motion and Surf on Sloping Beaches." (20 min.)

ACKNOWLEDGEMENTS

The author is indebted to the director (Dr. H. Rouse) and other personnel of the Iowa Institute of Hydraulic Research for the use of the flume and for their advice and assistance in the conduction of the experiments.

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XL

HEARING

Remarks by the Guest of Honor of the American Otological Society

Stacy R. Guild, Ph.D.

Baltimore, Md.

Mr. President, members and guests of the American Otological Society: The designation as Guest of Honor for this meeting of the Society is a distinction that I deeply appreciate, as I also appreciate Dr. McNally's extremely kind remarks in introducing me. Thank you, very much.

Our President, Dr. McNally, when he informed me of the honor, also asked me to participate in the scientific program of the meeting. His invitation gives me an opportunity, on a suitable occasion, to admit ignorance. This is, I believe, one of the privileges of a Guest of Honor. The ignorance that I admit concerns the topic I have chosen to speak about, namely, hearing.

For over 40 years my primary interest has been to learn how we hear. I have tackled some aspects of the problem myself, I have carefully observed the efforts of other investigators, I have read widely in the possibly pertinent literature, I have even listened intently at many meetings such as this one today. In spite of all this activity and the resultant cogitations and discussions, I still do not know how we hear. Furthermore, I am convinced that no one, as yet, knows how you are hearing what I am saying, or even how a simple auditory stimulus, such as a pure tone, is perceived.

Please do not misunderstand my admission of ignorance; I am pleading only a partial, not a total, lack of knowledge of how we hear. Many parts of the fascinating puzzle are known, more or less well, but many essential facts remain to be discovered. Today I shall not try to discuss the items of this topic that are known, or how completely each of them is known. I shall not even name the parts of the puzzle that have been satisfactorily identified or tell by what methods

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or by whom the original observations of them were made. Instead, I wish today to emphasize that the as yet unknown parts of the puzzle of hearing are of fundamental importance to an understanding of how we hear. The unknown items are, furthermore, so numerous that I doubt all of them will be found and the complete picture assembled during the years that may remain to me or to others of my generation.

Important advances in methodology have been made since I first became actively curious about the phenomenon of hearing. Each new or improved method of observation has made it possible for investigators to gather additional pieces of the evidence needed to explain how we hear. But the evidence is not yet enough, and I suspect that the discovery of some of the missing links in the story will have to await the development of new techniques by which to observe Nature, techniques and methods based perhaps on principles not yet recognized. For this reason, as well as for others, I believe it important that students of hearing should keep abreast, or at least aware of, developments in many fields of learning. Clues to possible new techniques for attacking the puzzle of hearing may come, as they have in the past, from unexpected sources.

A rapid increase in the number of persons seriously interested in the problem of hearing has occurred in recent decades. This increase in interest has been at such a rate and of such a magnitude that it merits description as an "up-surge"; in fact, no other word seems adequate to describe the phenomenon. This up-surge of serious interest in the topic is to me a most welcome sign, an omen that augurs favorably for the solution of the problem of how we hear. When I first became specially curious about how we hear, a year or so before the outbreak of the First World War, there were, in the whole western hemisphere, fewer investigators of the topic than I have fingers. Now, in contrast, the number of investigators in this field is so large that it has become very difficult indeed to keep up with the literature pertinent to the problem of hearing. The up-surge of active interest in hearing has not been limited to one or to a few of the aspects of the total problem; it has occurred in all aspects, from the purely morphological to the clinical, from physical acoustics to neurophysiology.

The increased interest that clinical otologists nowadays have in hearing, as compared to what they had when I first became acquainted with members of the specialty, is a healthy sign indeed, not only for the welfare of their patients with impaired hearing, but also for the

ultimate solution of the puzzle of what actually happens during normal hearing. For the members of this audience and of this Society I do not need to tell why and in what ways the welfare of their patients is served by the increased interest of clinical otologists in hearing. I wish, however, to expand the statement to the effect that the increased interest of clinical otologists in hearing may help to solve the puzzle posed by normal hearing. The clinicians are the ones to whom patients with impaired hearing take their troubles; they do not go for advice or help to an anatomist or a neurophysiologist or a psychologist or a physical acousticist, or to any other representative of the basic sciences concerned with hearing, no matter how well versed that person may be in problems of hearing. The result is that members of the basic sciences who are studying hearing seldom if ever have the opportunity that comes daily to the clinical otologist. The thoughtfully observant clinician, by telling basic scientists about the disabilities his patients have and the queries they raise in his own mind, can often be of real assistance to the basic scientists in their attacks on the problem of normal hearing. Co-operative and persistent interrogation and observation of Nature, by clinicians and by scientists, may yield information desired by everyone interested in hearing, whether it be normal or impaired hearing.

For the beginner in the field of hearing, who in spite of my statements still believes that we do know how we hear and who may wish I had supported my admission of ignorance with citations from the enormous literature on the subject, I recommend perusal of the following four items: a) Wever's book, "Theory of Hearing," published seven years ago; b) Wever and Lawrence's book, "Physiological Acoustics," published two years ago; c) Galambos' review article on "Neural Mechanisms of Audition," published two years ago (Physiological Reviews for July, 1954); and d) the paper by von Békésy on "Current Status of Theories of Hearing," published only one week ago (Science, May 4, 1956). If, after reading these four recent items, you do not join with me in admitting ignorance of how we hear, I will be surprised. And I shall hope that the experience will stimulate you into tackling personally some of the fascinating puzzles that remain to be solved in the field of hearing.

This brief address can be summarized thus: the puzzle of normal hearing remains unsolved, in spite of the efforts of the large number of investigators who have studied and who are studying aspects of the problem. The opportunities to contribue to knowledge of how

we hear are limited only by the techniques of observation presently available. For alert young investigators with new ideas, the field of hearing still offers a real challenge, not only in its basic science aspects but also in its clinical aspects.

JOHNS HOPKINS HOSPITAL

XLI

PURE-TONE AUDIOMETRY IN YOUNG CHILDREN; PSYCHOGALVANIC-SKIN-RESISTANCE AND PEEP-SHOW

PAGE STATTEN, M.D.

AND

D. E. S. WISHART, M.D.

TORONTO, CANADA

The importance of discovering hearing impairment as early in life as possible has been recognized for over 20 years but how to make the discovery is not yet settled. Our experience with two methods of using pure-tone audiometry in young children is the topic of this paper.

The first modern book on the development of the child was published by Gesell in 1925 and the latest report regarding that research appeared only two years ago. It has been proven that the first 12 months of a child's life is the period specially adapted to listening and the second 12 months to preparation for speech.

As a result, the urgency of utilizing this early life period to the maximum is becoming generally recognized. Educators in many cities are providing classes for preschool children. Advice on training methods is being given to mothers of infants suspected of having hearing impairment. No longer is there a postponement in having children investigated until they are old enough to co-operate with formal adult-type hearing tests: indeed, because of familial deafness, or possible prenatal influences, hearing evaluation is often demanded for infants.

Investigation is begun by history taking and examination. These procedures are of the greatest importance but are not included in

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this discussion except to say that the examiner must be on the lookout constantly for factors that may be affecting the middle ear, causing a conductive deafness or superimposing a conductive element on the perceptive deafness.

EVALUATION OF HEARING

It is apparent from the profuse literature on the subject that we have not yet found a scheme for the testing of hearing in adults that is universally acceptable. The testing of hearing of infants and preschool children is much more unsettled.

Some forms of adult testing may be adapted for use in co-operative children down to the age of five or six years. It is widely believed that this testing of the hearing of young children by pure-tone audiometry is so unreliable as to be nearly useless. For the unco-operative child and for the preschooler we must find a means of testing not requiring his co-operation, or we must adapt our tests to his abilities.

As will be seen in what follows, we have explored these two alternatives. In psychogalvanic skin-resistance testing—hereafter referred to as P.G.S.R.—the child's co-operation is not required. In peep-show testing, our tests are adapted to his abilities.

GENERAL OBSERVATIONS

We have learned from Gesell and his workers[1] much regarding the normal development of the child. The Ewings[2] have studied the development of hearing and speech in the normal child, and the variation in vocalization and response to sound stimuli in the infant and child with defective hearing. With children below the age of two years they have "found that the presence or absence of deafness can be determined by using a quiet voice at six feet as the principal form of stimulus, supplemented by a variety of sounds that tend to gain meaning for ordinary babies, such as quiet high-pitched rattles in plastic toys, the tinkle of a teaspoon against the side of a bottle or a cup, and light tapping on a door." In their experience "no child with a chronic hearing loss of significant extent, bilateral or unilateral, has been successful in locating the direction from which such sounds come, even if he has responded to them when made loudly enough to reach his threshold of audibility . . . as yet, they have not found it possible to determine with certainty the frequency-intensity characteristics of deafness in children under the age of two years."

DEVELOPMENT OF CONDITIONING METHODS

Pavlov's study[3] of conditioned reflexes has made the phenomenon familiar to all educated people. It is interesting to otologists that the auditory sense was used in his classic experiments with dogs—the bell, food, salivation. In 1927, Aldrich[4] used the conditioned response method with a three-month old baby, up for adoption; conditioned her to the sound of a bell by means of a pin scratch on the foot; and thereby established with certainty her ability to hear despite the fact that prior to conditioning there was no response to loud sounds made beside the ears.

From the study of conditioning there developed the two methods of investigation which form the basis of our study: P.G.S.R. audiometry and Peep-show audiometry.

DEVELOPMENT OF PSYCHOGALVANIC SKIN-RESISTANCE AUDIOMETRY

P.G.S.R. audiometry attempts to obtain pure-tone threshold audiograms in young children objectively.

In 1888 Feré[5] showed that man's skin-resistance to a weak electric current changed as a result of external stimuli. This is the basis of psychogalvanic skin-resistance audiometry. The skin-resistance varies with the activity of the sweat glands and is dependent upon the integrity of the sympathetic nervous system. The term psychogalvanic skin-reflex was introduced in 1909 by Veraguth.[6] Coombs[7] and Davis[8] showed that a sound stimulus must be strong to produce a response and its intensity is therefore not an indication of the amount of hearing and also proved that there is rapid adaptation to sound stimuli. However, Seward and Seward[9] showed that there is a comparatively consistent response to pain as compared to sound and that any adaptation may be overcome by increasing the intensity of the shock. Hovland[10] experimented with pure-tones as conditioned stimuli.

In 1947 Michels and Rondt[11] presented an objective method utilizing the galvanic skin response in differentiating organic from psychogenic deafness. They used an electro-encephalograph and presented several illustrative cases with graphic records.

It was, however, Bordley and Hardy, by taking the problem to Richter,[12] who established P.G.S.R. as an experimental and clinical tool for the testing of hearing. The name P.G.S.R. audiometry was

Fig. 1.

Fig. 2.

widely accepted. We see little advantage in changing the name as suggested by some writers.[13,14]

STUDY OF OUR P.G.S.R. AUDIOMETRY

Relatively early in the era of P.G.S.R. audiometry, through the kindness of the Atkinson Charitable Foundation (1951) we had a machine built to the specifications of that used at the Johns Hopkins Hospital. Modifications are presented below. From February 1951 to March 1956 we have performed over 250 tests. In normal hearing adults, we found we were getting results corresponding to those obtained with subjective pure-tone audiometry. We were able to use it successfully in older children.

As we approached the age and type of child with whom we thought we would get our greatest benefit, infants and unco-operative children whose hearing is exceptionally hard to estimate by other methods, our results became disappointing. We made a statement in 1953: "We found that in most cases in which we were unsuccessful

in testing by (other) methods, we were also unsuccessful with the P.G.S.R. We will continue to use the P.G.S.R. to determine whether it will become a useful testing method in our hands. It has the possibilities and with changes in technique and modifications of the apparatus we hope that eventually it will be more practical for us."[18] Our present study is a continuation of that reported at that time.

APPARATUS

The apparatus was built to the specifications described by Richter and Whelan.[19] It measures and amplifies the resistance between two electrodes placed on the skin and produces a graphic recording of its changes. A standard audiometer supplies pure-tones through earphones to the ears of the subject. A galvanic electric shock which can be adjusted is applied through a pair of electrodes placed in contact with the subject's skin (Fig. 1).

The equipment, mounted in a mobile wooden cabinet, consists of five basic units.

1. Pick-up—a modified Wheatstone bridge with a 4½ volt dry battery.
2. Amplifier—a General Radio 715A Direct Current Amplifier.
3. Recorder—an Esterline-Angus AW, 5 milliampere ink-recording ammeter.
4. Shock generator—a Harvard Inductorium with a 4½ volt dry battery.
5. Audiometer—a 2A Western Electric audiometer.

Two identical pairs of polished zinc electrodes are used: one pair—the skin-resistance electrodes—lead from the patient to the Wheatstone bridge circuit; the other pair lead from the shock generator to the patient.

The electrical changes in the skin vary with sweat-gland activity resulting from stimulation of the sympathetic nervous system. A current varying between two and twenty micro-amperes is induced between the skin-resistance electrodes: as they affect the currents of the Wheatstone bridge circuit they are amplified and recorded in ink on the recorder.

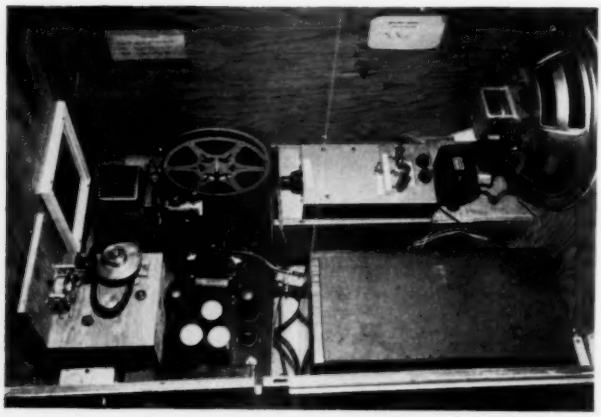

Fig. 3.

MODIFICATION OF THE APPARATUS

Our original equipment was identical with that described by Bordley and Hardy[20] except that it was fitted with a Western Electric 2A audiometer. Early in our studies we realized that it did not supply adequate intensity for many of our subjects. An amplifier and attenuator were added.

A control box with buttons for sound and shock stimuli was added. One button connects the audiometer to an indicator needle on the recorder; the other button connects the shock source to the other indicator needle of the recorder. Thus the time and duration of sound and shock stimuli are recorded on our graph along with skin-resistance activity.

Consultation with Dr. W. R. Franks, of the Department of Medical Research, Banting and Best Institute, resulted in an intensive study of the efficiency of our equipment (carried out by G. A. Meek, M.A.) and subsequent alterations, as follows:

1. A light four wire cable carrying both shock and sound leads replaced the separate electrode leads. A plug near the child allows the child to be disconnected easily without removing the electrodes.

The wire is long enough that the child's activities are not hampered, even if he moves around the room.

2. A three electrode arrangement was tried to see if the effects of muscle movement could be cancelled. No help was obtained by this study.

3. Various zinc electrodes—a wrap-around type for the finger and small round and rectangular pieces—were used and compared. As long as contact was maintained there was no choice between them. We use round polished zinc electrodes, one centimeter in diameter, soldered to the wire leads.

4. By comparison, the use of the jelly (electrode lubricant, used in E.E.G. and E.C.G. work) seemed as effective and easier to handle than the zinc sulphate paste used by Bordley and Hardy. We use it routinely.

5. To measure the effective skin-resistance at any time during the test a resistance decade box was made and connected with the Wheatstone bridge circuit. A reading of the resistance may be made at any time; the change in skin-resistance can be estimated with each sound or shock, by measuring the swing of the needle recorded on the graph.

6. Connections at the resistance box were altered so that one electrode to the child was at ground potential. This reduced the effect of contact with the child by persons or grounded objects, thereby reducing interference in our equipment.

7. The operating coils of the Esterline Recorder pen which were 110 volts were replaced by coils rated at 6 volt DC or 16 volt AC, 60 cycle maximum. A 12½ volt transformer was used to supply these coils. This removes 110 volt wires from the push button box and reduces chance of shock. The low voltage coils also decrease to nearly zero the small electrical effect on the recording pen which might be confused with a change of skin-resistance.

8. A light Telex plastic ear-set was tested and compared with standard double phones that had been in use. While its tone is not as free from harmonics, it seems preferable for small patients. A Telex twin-set allows easier application to the head.

The checking and modification of our apparatus by the Medical Research Department of the Banting and Best Institute assured us

that it was capable of accurate performance. We have found it most important to have an experienced technician available for maintenance of this equipment.

Our subjects include children who were too young for our peep-show and children who had been unsuccessfully tested by it and other methods. Among the latter were a few malingerers and a few who were wilfully unco-operative. Although our P.G.S.R. testing began in February 1951, this study is based on 122 tests on 101 children, during the period from October 1954 to March 1956, when our total hearing clinic load was 506 new patients.

Causes of hearing disorder in these children are shown in Table I.

TABLE I

P.G.S.R. SUBJECTS

Congenital or unknown deafness	22%
Suspicion of deafness with normal hearing	19%
Normal children with normal hearing	17%
Mental retardation	13%
Prematurity	5%
Meningitis	4%
Maternal rubella	4%
Rh incompatibility	4%
Middle ear disease	4%
Hereditary deafness	3%
Others	5%

Ours is not an academic study, but rather one to demonstrate the value we have or have not received from the P.G.S.R. in the handling of our hearing clinic load. As will be shown, our results in testing the hearing of most young children have been perfectly satisfactory with our peep-show technique. We reserved P.G.S.R. testing for those cases in which we felt the need for additional information.

Our team of investigators consists of an otologist, a pediatrician and a child psychologist: and a senior technician from the Department of Physiological Hygiene of the University of Toronto.

Our test room is plain and bright. A minimum of equipment is seen. The area for the child may be closed off with moveable curtains. There is a table for toys, and space for a play-pen or a bed. The cabinet containing the apparatus is out of sight behind the child and may be hidden by a curtain. For certain children a loud speaker can replace the earphones.

TECHNIQUE OF CARRYING OUT THE TEST

Skilful handling of the child to gain good rapport is essential to the successful performance of the test. This has been stressed by Hardy and Pauls[21] and other workers.

A child finds a hospital strange. This is especially so in the pre-school group. With this in mind the child is seated on a small chair at a small table or held on the mother's or assistant's lap and toys are given or shown to him. Some children are more relaxed while playing on the floor: for this reason we have a play-pen available. Other children are observed and tested in their beds or cribs. The long electrode wires allow freedom of movement. While playing with the child a general impression is gained of the child's responses to conversational voice, clapping of the hands and calibrated noise-making toys. The child's reaction towards this particular visit is noted: whether he is shy, playful, aggressive or belligerent.

The skin-resistance electrodes, coated with electrode jelly, are then applied to the first and third fingers of one hand with adhesive tape. In infants the sole and dorsum of the foot may be used.

Usually this procedure is simple as most children are either indifferent to it or are pleased with the bandage. An occasional child associates injury with adhesive tape and must be persuaded that the zinc plates are not going to hurt. The shock electrodes are similarly applied to the calf.

The child is connected in circuit and a measurement of skin-resistance made. The skin-resistance stabilizes while the child plays and becomes accustomed to the assistant and his surroundings. The graphic pattern for this testing is roughly noted; most often it is wavy with a few spikes and little drifting. The random changes are a result of the child's alertness or interest in his surroundings. If he tends to become drowsy the basic pattern becomes flattened and the skin-resistance rises; if strangers enter the room the graph becomes agitated and the skin-resistance falls.

When the graph has stabilized the earphone is applied, causing slight fluctuations in the skin-resistance. Most children tolerate the light plastic ear-piece but an occasional child has to be reassured and then entertained to distract him from the wires now leading from his ear, his hand and his leg. If the child is too upset the loud speaker may be used.

Theoretically the child should now be in a position to be conditioned. Some are so upset, however, that sound alone is used, and shock is not used at this sitting. An attempt is made to gain and retain some rapport with the child for future tests.

Our first attempt at measuring hearing is by using sound as the direct or unconditioned stimulus. Sounds are made in the ear, beginning with a 512 cycle tone at 10 decibels. The intensity is increased in 10 db steps. When the sound becomes loud enough it nearly always shows graphically, clinically or both graphically and clinically. Graphic evidence of a response appears after a delay of one to three seconds. It is a characteristic wave imposed on the continuous record of skin-resistance activity. A child tends to hesitate in his play to listen for the next sound. The intensity is then lowered by steps until the response disappears. It is raised again until it shows. On many occasions we find in retrospect that the sound noted in the above manner is close to threshold.

When it is certain that the child hears sound, conditioning is attempted. A 512 tone well above our estimated threshold is presented. This is followed in a few seconds by a shock. If there is no graphic or clinical indication of reaction to this shock the intensity is increased. If a child will become conditioned it usually occurs after about ten sound-shock sequences. The interval between the sequences depends upon the reaction on the child and graphic evidence that the skin-resistance is stabilizing. The usual interval is 15 seconds. When conditioning occurs the shock is omitted. It may be necessary to use it again and perhaps at a higher intensity, for reinforcement.

The shock itself may eventually fail to give a change in skin-resistance too. This is due to adaptation to the shock. Hence, conditioning may be obtained, but threshold hearing not estimated, because of difficulty in maintaining the conditioned response.

When a response to sound is evident the intensity is lowered by steps until it fails to give a response; then it is raised until the respone reappears. This is considered threshold for this tone.

Similar tests are made for 1024, 2048, and 4096. The procedure is repeated for the other ear. Many sittings may be necessary to complete the threshold levels.

The time of the sound and shock are recorded on the graph and the tone and its intensity, clinical responses and a decision as to whether the response was considered a response to hearing are inserted.

The child's attention can usually be held for a 15 to 25 minute period; then the child is either restless or drowsy and the test must be interrupted.

Our observations are recorded on this form.

TABLE II

P.G.S.R.

Date:
Name:
History No.: Sex:
Birthdate: Hg. Clinic No.:
Admission Diagnosis: Age:
Reason for test:
Probable cause of deafness:

Skin electrodes a) type
b) position
c) spacing

Shock electrodes a) type
b) position
c) spacing

Type of phone a) headphone
b) hg. aid
c) loud speaker

Skin Resistance a) steady
b) wavy
c) drifting
d) other

Measurement of resistance a) initially b) terminally
Intensity of Shock (range)

Responses

Unconditioned reflex—Sound (ohms)
—Shock initially terminally

Conditioned reflex—Type of conditioning a) consecutive
b) coincident

—Ease of conditioning a) easy
b) difficult
c) not at all

No. of conditioned responses obtained—
Reinforcement necessary Yes ..... No .....
Manner obtained—
Duration of test /

Behaviour of Child

apprehensive	restless	playful
excited	alert	quick
quiet	co-operative	slow
inert	attentive	played with toys
cried	frightened	other

Results of Tests:

Date	Type of Test	Right				Left				*Comments*
		512	1024	2048	4096	512	1024	2048	4096	

Assessment of Testing:
Reasons (if unsatisfactory test):
Comments:

At the conclusion of the test the results are transferred to a standard audiogram.

COMMENT AND EVALUATION

The criteria for successful P.G.S.R. results are difficult to establish because of the complexity of the test and the variability of the physiological reactions. To give an answer to the part played in the testing of hearing of young children by this method we will discuss in order:

1. Apparatus
2. Skin-resistance measurement
3. Conditioning
4. Response to sound
5. Response to shock
6. Graphic response
7. Objectivity—importance of the experience and judgment of the examiner.

1. *Apparatus.* The components of the apparatus must be properly assembled and maintained to reduce to a minimum errors that could arise from variations in current and outside interference. The operator must at all times be alert to unusual performance. He must be able to make the proper adjustments or have trained technical skill available.

2. *Skin-Resistance Measurement.* The first physiological principle involved in P.G.S.R. is skin-resistance. The resistance measured is not a true resistance in the sense defined by Ohm's law, as it is not independent of current and applied voltage. It is an effective resistance and measures ease of transportation of ions through the skin.

As already stated, it varies with individuals and in the same individual in various emotional phases. It changes in response to outside stimuli. Measurements and variations encountered in our study will be given.

In children over five years of age skin-resistance ranged from 2,000 ohms to 140,000 ohms. In all but four there was an appreciable fall during the test. In three of these it remained around the same level; these children were well adjusted and co-operative throughout, and all had hearing impairments. In the fourth, the skin-resistance rose slightly; this child was very shy and withdrawn, before, during and after the testing.

In children under two years of age the skin-resistance measured from 6,000 ohms to 900,000 ohms; most were recorded below 100,000 ohms.

Again in most instances the skin-resistance fell during the testing; in seven, the skin-resistance remained the same and in one, rose.

Of the seven whose skin-resistance remained the same, four had normal hearing and development, three were retarded and had slow responses with impaired hearing. One of the retarded children had been quite heavily sedated prior to the testing, so much so that she responded only to painful stimulation: her skin-resistances measured 900,000 and did not vary significantly. One of the children with normal hearing whose skin-resistance did not vary had ichthyotic skin. In both instances repeat testing showed a more normal skin-resistance and the skin-resistance fell during the test. In the one instance during which skin-resistance rose, the child was quiet and had normal hearing.

In children, between two and five years the skin-resistance ranged from 1,000 to 750,000 ohms. Most skin-resistances measured between 20,000 and 100,000. In all but nine cases, skin-resistance fell appreciably during the testing. In six cases the skin-resistance did not change. Three had hearing impairment and three had normal hearing. All six were quiet, co-operative, even playful in two instances, during the test period. In three instances the skin-resistance rose. Two of the three had impaired hearing and cried and fussed during the testing; one child had normal hearing and was disinterested in his surroundings and quite uncontrollable.

One child with severe eczema had the lowest skin-resistance measured. This was 1,600 ohms at the commencement of the test and 1,000 ohms at the completion of the test.

In general the skin-resistance in children does not vary too much with the age of the child. The average range is between 20,000 and 100,000 ohms. The usual pattern is for the skin-resistance to fall an appreciable although unpredictable amount during the testing.

Children with abnormal skin, such as ichthyosis, eczema, tend to have skin-resistance above and below the normal range. Children with slow development and restricted emotional development such as schizophrenics and emotionally disturbed children tend to have normal skin measurements, patterns and responses.

The actual measurement of the skin-resistance tends not to affect the test situation. With high measurements the magnification of the ohmeter must be increased in order to measure similar changes that are readily seen when the skin measurement is within the average range. Usually the skin-resistance will fall to levels which show readily without greater magnification.

In children whose skin-resistance remains the same throughout the testing, it is often found that they have been quiet and co-operative throughout the testing period.

3. *Conditioning.* Conditioned reflexes were classically described by Pavlov in 1927. He described them as "phenomenon of common and widespread occurrence; their establishment is an integral function in everyday life. We recognize them in ourselves and other people or animals under such names as 'education,' 'habits,' and 'training'." He used very simple examples in dogs to illustrate conditioned reflexes. In this work we are attempting to employ the broad princi-

ples of education, habits and training to a simple procedure of association of sound with shock; but the conditioned reflex itself is complex.

In our study 50 per cent of the children, in whom conditioning was attempted, conditioned. In 25 per cent the conditioning was straight forward with a prompt association between sound and shock that was maintained for an utilizable period. The majority of these children were of an age to understand, showing that educability is a factor in successful conditioning. Two of the children were under two, however; so it is not the sole factor. All these children were playful and co-operative. In 25 per cent the conditioning was not maintained to the end of the test, even with reinforcement of the shock. If there was still an association between sound and shock it was not made apparent to us visibly or graphically.

In the other 50 per cent of the group in whom conditioning was attempted there was no evidence of conditioning. Most of these children were difficult; some were bright and co-operative; but for some inexplicable reason the conditioning failed. Up to 25 sound-shock stimuli were given without evidence of association.

We found in 10 per cent of children there was no consistent change in skin-resistance, to either sound or shock although they were conditioned clinically. By this clinical conditioning the hearing was assessed.

The primary requisite for conditioning, according to Pavlov, is: "The animal must be alert and in good health, and there must be complete freedom from all simultaneously operating nervous influences." This state, from our experience, would seem to be the primary requisite in man, too.

A child however who has had a long journey or has foregone an afternoon nap is not in an alert state and is very difficult to settle and reassure; a child who is sedated is not responding to stimuli normally; a child who is hungry or uncomfortable will not condition readily. Much can be done to assure an alert child but those that are tired, irritable or fretful throughout the test period are difficult subjects.

From this study we find that age plays some part in conditioning but it is not a limiting factor. Hearing impairment is not a factor in conditioning as long as the stimulus (sound or vibration) is adequate. An alert state aids conditioning.

4. *Response to Sound.* Sound may be used as an unconditioned stimulus[13,22] or as a conditioned stimulus associated with shock. The unconditioned response is similar to the "startle reflex" theoretically, but in practice, due to the sensitivity of the changes in skin-resistance response, a graphic change may be recorded at or close to threshold. We have found the unconditioned response so valuable that in many cases we find it unnecessary to use conditioning. We have been able to show in some cases by retesting, that the unconditioned sound gave us threshold values.

The little understood vibration sense seems to play an important part in the severely deaf. Vibration is similar in many ways to sound physically and in its effect on man: both have frequency and intensity by which man's sensitivity is limited. As we approach the upper limits of audibility for any frequency there is a greater vibratory sensation. We feel that in many cases in the extremely deaf when our sound intensity is very high, we are actually performing a P.G.S.R. test on the vibration sense.

Some children we have tested—mentally retarded, aphasic and autistic—appear to be impervious to sound, and seem to experience no sensation from pure-tones. This was also stated by Barr.[23]

5. *Response to Shock.* The galvanic shock from the Harvard inductorium produces a sensation that may be uncomfortable or painful. We attempt to make it a mere discomfort and yet it may be disturbing to a child. Some children are so upset by the initial test procedures that we find it wise to omit the shock and make our observations from the unconditioned sound response alone. If the shock is not of sufficient strength it will not produce a graphic response; if it is too strong the child will become upset and rebel. As no two children have the same pain threshold, the proper intensity must be found for each, by gradually increasing the shock until it shows graphically. Some children feel the shock intensely, as evidenced by wincing and withdrawal of the leg, with no graphic change being produced: they respond clinically. In others a response to an initial shock may be recorded graphically, but later the same shock may have no obvious effect; increasing the intensity may again produce a response, but again it may disappear. This is evidence of adaptation to shock.

6. *Graphic Response.* The graphic representation of the normal skin-resistance activity was typical in nearly all cases: the basic

pattern was steady or wavy; responses to external stimuli were superimposed; it was usually not difficult to identify the characteristic waves of the presented sound and shock stimuli. An atypical graph, showing spikes rather than waves, was recorded for a mentally retarded child with a spastic paraplegia and hearing impairment.

If the apparatus is in order, if the child is conditioned readily to sound and shock, if both stimuli elicit responses in skin-resistance, if a graphic response is obtained, and if an audiogram is plotted, the result is a successful P.G.S.R. hearing test (Table III).

TABLE III

RESULTS OF P.G.S.R. TESTING ACCORDING TO GRAPHIC RESPONSES AND AGE

	Under 2 years	2-5 years	Over 5 years	Total
Group I	2	5	8	15
Group II	31	45	11	87
Group III	6	14	0	20

Group I —Successful. Child responded to sound and conditioned readily.

Group II —Partially successful. Clinical assessment was necessary. Child responded to sound and conditioning difficult to impossible or conditioning not attempted.

Group III—Unsuccessful. No response to sound or shock graphically. Child resisted earphones or electrodes.

Applying such exacting requirements to our study of 122 tests on 101 children we were disappointed in our results: only 15 or 12 per cent qualified as successful tests. However in an additional 87 or 72 per cent the graphic response was helpful in arriving at the hearing threshold and the tests were considered partially successful. In 20 or 16 per cent there was no useful graphic response and the tests were deemed unsuccessful; in about one third of this group, however, without the help of graphic responses, a clinical evaluation of hearing was made.

Unsuccessful tests included a few unmanageable children who did not tolerate the electrodes or earphones.

7. Objectivity. Importance of Experience and Judgment of Examiner. P.G.S.R. audiometry has been described as an objective

method: it approaches objectivity when the subject conditions readily, showing typical waves after the proper latent period in response to sound. Even in these cases some clinical judgment is required to detect true responses. Stewart has attempted to overcome this difficulty.[24]

As pointed out by Goodhill,[13] a truly objective test would require direct recording of cochlear microphonics or action potentials from direct electrode applications to the inner ear or the VIII nerve as responses to acoustic stimuli delivered to the external ear.

In our experience with exceptionally difficult children we find that the experience and judgment of the examiner assumes a much greater importance than the graphic response, in interpretation of results. All tests gave us information. For the majority, the results are based on combination of graphic responses and clinical judgment. Rarely are graphic responses sufficient.

PEEP-SHOW AUDIOMETRY

Peep-show audiometry attempts to obtain pure-tone threshold audiograms in young children subjectively. In 1928 Ewing[15] introduced the conditioned reflex as a means of testing hearing with the "tunnel-test." This led to the peep-show technique of Dix and Hallpike[16] whose authors state that a child should have reached a mental age of three years to be suitable for testing by this method. Wishart[17] copied the peep-show and modified it greatly.

Changes in and additions to the apparatus necessitated alterations in technique. The method of using it, presently to be described, is our most useful method of testing the hearing of the preschool child.

The testing can be performed by one person—although we often allow the mother to sit by the child and help.

Apparatus. Our peep-show is in the form of an attractively colored doll's house (Fig. 2). It contains a standard 6BP Western Electric audiometer with earphones. A loud speaker has been mounted on it. Incorporated in it is a movie projector (Fig. 3) which throws an image on a ground glass screen situated down the hallway, inside the open front door. Over the doorway is a porch light and beside it is a door bell.

A control panel is provided to allow the examiner to produce intermittent tones of standard frequencies and intensities from the

audiometer through the loud speaker, or through the earphones fitted to either ear (see Fig. 2). When the tones are being sounded, pressing the door bell will start the motion picture. When there is no sound, the door bell is not effective. The child sits in front of the doorway where he can see the ground glass screen. The examiner sits beside the house where he can observe the child's responses. His hands controlling the audiometer and the panel are not seen by the child.

Technique. Many of the children presented to the peep-show are believed by their parents to be deaf. Practically all of them are unable to follow verbal instructions. Many, however, are curious. Such a child is allowed to investigate the front of the peep-show without any guidance and will often find out by himself what happens when he presses the door bell—namely, that a moving picture appears at the end of the hallway. That is lesson number one.

He is then allowed to keep pressing it himself—and his interest is obtained.

While the child is so amusing himself, the 512 tone is sounded intermittently and increased in intensity until the child shows that he is aware that something is happening. Then he is helped to discover that, when this mysterious something is not happening, the movie will not start. By demonstration the association of the sound and the running of the picture is related to him. He soon waits until the sound is being produced before pressing the button. He has learned lesson number two. He is now conditioned.

To aid conditioning, a visual signal may be used as well, by setting the porch light to go on and off with the sound. Of course, when conditioning is established the light is turned off and the sound stimulus alone is used.

The movie we are using has been produced especially to hold the interest of the child. It is in color and was taken on a farm showing familiar animals and scenes. We felt some children might be frightened of the activity of a movie and so provided a slide projector to show colored still pictures but we have found the movie much preferable.

The child is initially conditioned through the loud speaker to a 512 tone well above his estimated threshold. When we are sure of the conditioning, the intensity is reduced by 5 db steps. When there is no response, the intensity is raised by 5 db steps until a response

occurs again. This is considered the threshold for this tone and is plotted on the peep-show audiogram chart. The conditioning, if established, continues for the other frequencies and threshold levels are obtained in a similar way so that the complete audiogram is finally charted. This is a free-field pure-tone threshold audiogram.

In suitable children the earphones may now be used to make an audiogram in a similar way for each ear. A bone conduction audiogram may also be made for older children when indicated. To record our findings and observations we use a printed form designed to record four tests.

COMMENT

Not only is the peep-show the favorite apparatus in our clinic for doctors but its use dramatically demonstrates to the observing parent the child's hearing capacity for pure-tones. It leaves no question in his mind regarding the ability or disability the child has in hearing. With our machine the child is attracted, his attention is held, there is nothing to distract him, he teaches himself to obtain the results we desire and the oftener he returns to the clinic the more enthusiastically he runs to our peep-show.

The type of conditioning described is limited in its use by the age, intelligence and co-operation of the patient. We introduce every preschool child over 18 months of age to the peep-show testing. We have threshold audiograms of one child 19 months, and one 20 months, that were verified subsequently.

Evaluation. Records of 204 consecutive children tested with the peep-show have been reviewed. We have arranged them to show the ages at which we have been successful in our initial testing.

On two children under the age of two, out of a group of 27, we were able to make satisfactory audiograms. We were successful in 19 of 44 (or 43 per cent) of 2 year olds; 41 of 52 (or 80 per cent) of 3 year olds; 39 of 42 (or 93 per cent) of 4 year olds; and 35 of 39 (or 90 per cent) of children 5 and over (Table IV).

This analysis does not include any repeat testing taking place in a child returning at an older age; many of those under two had successful tests subsequently.

Causes of hearing disorder in these children is shown in Table V.

TABLE IV

RESULTS OF INITIAL PEEP-SHOW TESTS

AGE IN YEARS	TOTAL	SUCCESSFUL	PARTIALLY SUCCESSFUL	% SUCCESSFUL AND PARTIALLY SUCCESSFUL	FAILURES
under 2	27	2	0	7.6	25
2	44	15	4	43	25
3	52	38	3	80	14
4	42	38	1	93	3
5 & over	39	35	0	90	4
Total	204	125	8		71

Many of the children that we failed to condition have subsequently been found to be completely or severely deafened and without appreciation of the sound stimulus. Tests on children with low intelligence, brain damage, or severe behavioral problems were often classed as failures. Age and development are certainly limiting factors in any learning process, even a conditioned one. From many of the children whom we failed to condition, much information was obtained about the hearing, and also about the intelligence and behavior.

Experience with any technical procedure produces interesting new facts and leads to many improvements in methods. In some of our early tests we obtained audiograms that later on were found

TABLE V

DIAGNOSIS OF PEEP-SHOW SUBJECTS

Unknown or congenital deafness	39%
Meningitis	17%
Mental retardation	9%
Hereditary deafness	8%
Rh incompatibility	6%
Maternal rubella	3%
Congenital deformities	3%
Middle ear lesions	3%
Aphasia	3%
Prematurity	2%
Other	7%

to be too favorable. Retesting made us aware that some signals were being obtained by vibration rather than by sound. Severely deafened children are more alert to vibrations than those with moderate or no hearing impairment. Careful insulation of the loud speaker and parts of the doll's house touched by the children eliminated these false results.

The results of our hearing evaluation by general observations and by our peep-show audiometry enables us to outline an educational program suitable to the needs of all but a few children seen by us.

Enough time has passed for practical confirmation of these findings, as we see these children making excellent use of their residual hearing.

SUMMARY

We have presented a study of P.G.S.R. and Peep-show audiometry in the testing of the hearing of young children at the Hospital for Sick Children, Toronto.

The development of the conditioning method in the testing of hearing has been traced and also its application to obtaining pure-tone threshold audiograms by two methods—one not requiring the patient's co-operation (P.G.S.R.) and the other adapted to the child's ability to respond (Peep-show).

P.G.S.R. audiometry, based on the Feré skin-resistance effect and the Pavlovian conditioned reflex phenomenon, as practiced by us, is fully described. Modifications in the original apparatus are given in detail. Discussion and evaluation follow—based on our observations in testing young children. Our experience has been gained from over 250 tests in a five year period and this paper reports an intensive study of 122 tests on 101 children seen in the past 18 months. Varying and interrelating factors have been encountered and are discussed under headings—e.g., apparatus, skin-resistance, conditioning, response to sound and shock, graphic response and objectivity pertaining to the importance of the experience and judgment of the examiner.

In nearly all cases P.G.S.R. testing helped us form an opinion of the child's hearing. The opinion was reached in most cases by combining the graphic response and the clinical judgment.

Peep-show audiometry in which conditioning is obtained by rewarding the child with a pleasant experience for his response to

sound is presented in less detail. The peep-show, in the form of an attractive doll's house containing an audiometer and projector, is described. We show how the child is attracted and his attention held as he teaches himself to obtain the results we desire. The results show its limitations with regard to age, development and co-operation.

Our children, if old enough, are routinely tested with the peep-show. When the results are unsatisfactory or if further information is desired we use the P.G.S.R. Obviously, since different types of children are being tested by the two methods, the results cannot be compared.

CONCLUSIONS

As the majority of children may be tested by the more pleasant method, P.G.S.R. is necessary only in the very young and in those in whom examination is rendered difficult by development and wilfulness.

P.G.S.R. testing is difficult and may be an unpleasant experience for the child. An experienced, skilled team is essential—a team in which every member is aware of the principles involved, the limitations of the technique, and has a thorough understanding of the handling of the child. Therefore we condemn, with all our might, the indiscriminate distribution of this complex equipment under the assumption that it is a practical method of testing the hearing of any child by any operator. It can only become a practical method if the research of those recognizing its principles and difficulties continues.

As failures in conditioning are frequent and as changes in skin-resistance in response to stimuli are inconsistent, the effectiveness of this method may prove to be limited by the variabilities of the physiological reactions which form its basis.

200 St. Clair Av. W.

170 St. George St.

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XLII

INTRAVASCULAR AGGLUTINATION OF THE BLOOD:

A FACTOR IN CERTAIN DISEASES AND DISORDERS OF THE EAR

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Contrary to one of my undesirable tendencies I shall endeavor in discussing this subject to concentrate on a few points and refrain from expanding over much on the wider implications which come to mind.

First, a few remarks about clotting.

Throughout the ages clotting of extravascular blood has appeared to be such a common and expected phenomenon that it has been taken for granted. Mostly the reasoning went: coagulation stops bleeding and lack of coagulation is conducive to prolonged bleeding. What could be more simple, and until comparatively recently clotting has been thought of as a simple phenomenon. But it is not simple; other tissues than blood can clot and both blood and lymph contain fibrinogen and both clot; the blood more firmly than the lymph.

Clotting, like all biological mechanisms, has evolved from the beginning of life on earth; it varies in different individuals, races, species, with sex, and even with age, and the type of wound. Kenton[2] discovered that the fibrinogens of different species not closely related are species specific, as are other blood proteins. Thus was provided a biological means of differentiating proteins used to produce antibodies more delicate than chemical analysis in vitro.

The fact that in certain vertebrates there is rarely an agglutination, and no coagulation of the blood in the normal sense, and that generally the arrest of bleeding from small closed wounds requires

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My statements concerning extravascular clotting are based largely upon a recent book by Biggs and Macfarlane.[1]

only a few seconds (the bleeding time), whereas from open wounds hemostasis through coagulation may take five to ten minutes, indicates that the mechanisms involved in clotting can be various.

Although many hypotheses have been suggested, and a few facts determined, facts and fancies have been so intermingled, and the terminology become so multiple that much confusion has resulted. The main difficulty has been an inability to use any of the phenomenon of clotting but fibrin formation as an indicator, and unfortunately the living red blood cell is achromatophile, and freshly formed fibrin does not stain. No other observed change (physical or chemical) takes place during coagulation of blood with the possible exception of a viscid sticky platelet agglutination, and all this is the end result of a long chain of reactions.

Fibrin ferment (thrombin), the active coagulant of fibrin, appears in the blood during the formation of the clot, and fibrin formation is important although other mechanisms may be substituted for it. Does thrombin normally exist in the plasma? If so, in what form does it exist? How does clotting occur without prothrombin, as it does? How does it happen that a deficiency of fibrinogen rarely causes faulty clotting? There are many divergent opinions as to the nature of prothrombin and as to the presence of other clotting factors in the blood. You can not well measure a substance whose nature is in dispute, or one whose very existence is in doubt. Although natural extravascular coagulation occurs only in the presence of the morphological elements present in normal or pathological blood, many coagulation studies have been carried out in the complete absence of such elements. Moreover clotting in disease can be quite different than clotting in health.

Although from the scientific standpoint all phenomena, all biological processes, are complicated and difficult to describe in simple words, we can use simple words to record our observations. This I shall do.

Intravascular clumping, or agglutination (sludging) of the blood, although less spectacular, is clinically far more important than extravascular clotting or abnormal bleeding, and unfortunately little is known about it. It is believed that like extravascular clotting it may be useful as well as dangerous. As generally observed it has been thought of as a form of clotting, but in several respects it is quite a different phenomenon.

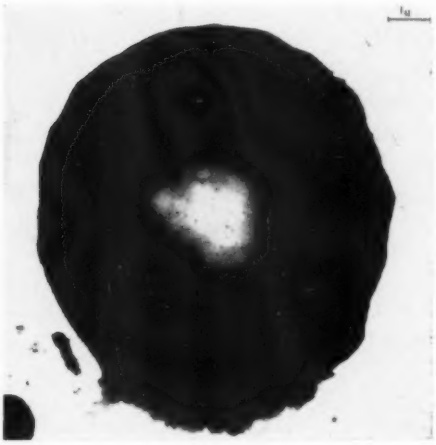

Fig. 1.—Electronmicrograph of normal erythrocyte (human) showing sharp interface. The crystals on the film are salt crystals from the Ringer's solution in which the cells were suspended.

In the first place active thromboplastin (one of the activators of prothrombin) is absent from circulating blood perhaps because for its formation several minutes' contact with some foreign surface is necessary. It may be that if the blood is circulating as it usually is when sludging occurs, the activating factors, except in certain instances locally, will be diluted to a nonoperative degree. Also there is a spontaneous fibrinolytic activity in human blood which is evident following severe shock, trauma or mental distress,[1] and this may inhibit clotting but it does not inhibit sludging. In the second place the tensile strength and density of intravascular conglomerates is much less than in fibrin clots. In the third place sludge is observable in the absence of bleeding; in the fourth place unlike clotting, sludging is occasioned by psychic or somatic shock, stress and frustration even of seemingly small degree. It may follow trivial surgical operations. True extravascular clotting has not been shown to primarily result from such strains, in fact the reverse occurs so that the greater the degree of shock the less may be the proclivity to clotting. In the fifth place sludging can and usually does occur in the absence of

Fig. 2.—Electronmicrograph of normal erythrocytes (human) chrome shadowed; alteration in shape does not produce a fuzzy interface. (Compare with 3 and 4)

clotting, and vice versa clotting can occur in the absence of sludging, or at least sometime before any sluding is detectable.

When sludge appears in the arteriolar capillary bottle necks or in arterioles, capillaries and venules, it usually pushes through with little delay, and although the circulation to the immediate area be impeded to some extent it usually is not permanently stopped. When the circulation is permanently stopped a fibrin clotting occurs. Even markedly sludging blood often appears to impede the capillary circulation but little and but little affect the rate of flow in the capillary beds of the tissues adjacent to the vessels involved. There appears to be a large tolerance; a critical threshold below which it is fairly well tolerated, no clinical effects being apparent, but above which threshold of tolerance the trigger is pulled and often an explosion occurs with devastating effects. There appears to be a series of critical thresholds of tolerance with chronic anoxias.

It is the consensus of opinion that although severe intravascular agglutination must to some extent affect all tissues of the body in differing degrees and with differing time intervals, and that although

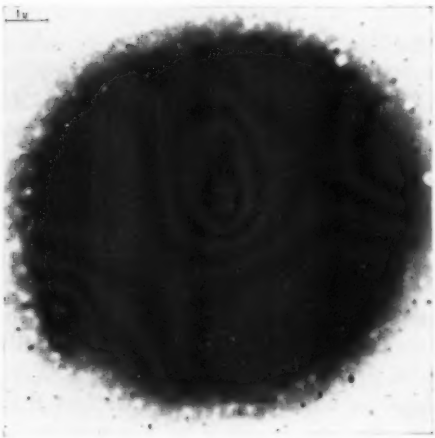

Fig. 3.—Electronmicrograph of an erythrocyte showing abnormal interface from a case of bronchopneumonia.

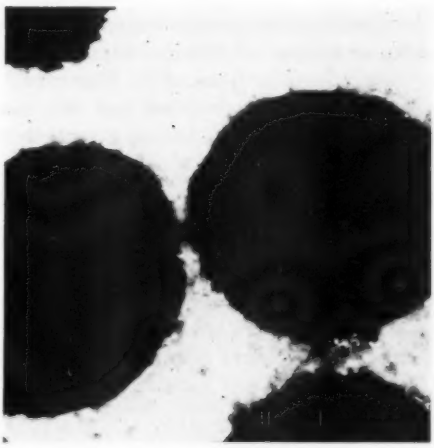

Fig. 4.—Electronmicrograph of human erythrocytes from a case of bronchopneumonia showing abnormal interfaces.

sludge is seemingly evenly distributed in the gross this does not rule out irregularities in its distribution.

Blood serum contains clotting factors as well as anticlotting factors, and factors for dissolving fibrin when fibrin is apparently no longer useful. However, a substance isolated from serum may have little or no resemblance to its prototype in the plasma, so that it is difficult to correlate the findings in these two media.

I infer that there is no fibrin in sludging blood because otherwise the masses would be less friable and less mobile and compressible. They would be unable to be squeezed into strips or stacks of blood cells approximately only 8 μ in diameter, and such squeezing is necessary if the masses are to be easily pushed through contracted arterioles and their capillary beds. On the other hand free, firmly clotted blood (thrombi) can only with difficulty, if at all, be pushed through the smaller bottle necks in the circulation. Therefore thrombi are prone to lodge in the smaller vessels and if by happenstance or because of a particular vessel anatomy in some tissue, and especially in tissue in an end organ with terminal arterioles, these vessels and the area they supply are shut off from the circulation suddenly and permanently (an apoplexy) or for a sufficient time degeneration and its sequelae ensue.

Searching the literature uncovered little or no information concerning the presence or absence of fibrin in intravascular agglutinates. It seemed to be "just taken for granted." However I wrote to Dr. Melvin Knisely and told him my opinion and this pioneer in intravascular research replied that, ". . . there is no reason to assume that fibrin per se is present in any kind of blood sludge thus far known to exist." For the present at least I seem to have guessed right.

Everyone agrees that an impedance of the circulation causes edema and interferes with metabolism, and especially with oxygen transfer, and the removal of wastes, but no one has said how much anoxia occurs or how much is necessary to produce disease or symptoms of oxygen deficiency. There briefly you have the picture as it appears to date, but not the whole picture. Let me sketch in a few details.

In Science, 1947, Knisely's paper (et al) on sludging of the blood[3] and recently Edward H. Bloch's monograph[4] impressed me greatly, and especially the implications of the observations in certain disorders

and diseases of the ear, namely, otosclerosis, tinnitus, vertigo, sudden intermittent or progressive partial or total deafness, Ménière's disease (hydrops of the labyrinth) and in certain other types of neural deafness, especially that accompanying aging. Also of course intravascular agglutination would appear to explain many other diseases of the tissues, within and without the ear, in the eye and other sense organs, in the brain and neural mechanisms, and in endocrin and digestive malfunctioning. Most somatic or psychic phenomena could be and in my opinion are accompanied by and affected by the different kinds of intravascular agglutinates, and of course by the neurovascular phenomenon occurring with them (and vice versa).

Remarkably small stimuli suffice to produce clinical symptoms in susceptible people, and in all people if they are sufficiently continuous or sufficiently recurrent.

It is not generally realized that it is unnecessary to completely cut off oxygen to produce neural deafness. Wever's[5] experiments measured the degrees and durations of hearing loss produced by oxygen hunger in animals during various time intervals, and in these animals the circulation was not shut off. It would be illogical to think that similar losses in hearing would not occur in humans who suffer from an anoxia affecting the cochlear sense mechanisms.

Similarly a dearth of oxygen in the static labyrinth would produce dizziness and a vertigo suggesting that one or more of the semicircular canals were involved, or the maculae. As with all disorders and diseases there will be marked differences between individuals because of inherited constitutional or acquired sensitivity to anoxias. There will be marked differences in energy reserve.

Not only the end organs are susceptible to anoxia caused by an impedance to their blood flow, but also their supporting and surrounding structures in the soft and bony tissues of the petrous bone, the otic capsule, and especially the promontory. In my patients with otosclerosis I have found not a single one who did not reveal intravascular agglutination, and this was marked following periods of emotional stress and increasing deafness, such periods being interpreted as coinciding with active phases of the lesion. Was this merely coincidental? I think not. Accumulating data appear to support this opinion.

Now let us consider to what extent the sludging mechanisms may cause local anoxia in the temporal bone and in its contained end

organs, keeping in mind that oxygen not being stored in the body must be continuingly acquired in the lungs and carried to the tissues by the blood. Also bear in mind that to function properly the red blood cell must travel singly, not in masses, and that although agglutinated blood appears to retain much hemoglobin its oxygen is depleted or lost, and it may not be fully regained. No one has determined how much hemoglobin or how much iron is retained in the sludged masses. Also keep in mind that sludging not only smothers the red blood cells, it also may affect the metabolism of the blood plasma, and of the lymph. Keep in mind that sludging should be considered as a part of the phenomena accompanying and in fact regularly caused by excessive contraction of the small blood vessels, and not as the only pathophysiology following neurovascular disturbances.

To recapitulate, both contraction of the small vessels and sludging impede the circulation to the contiguous tissues in different people in varying degrees at varying times, and the aggregates occupy comparatively a greater percentage of the space in the small vessels, the arterioles, capillaries and venules than in the larger vessels because they are packed more firmly in the smaller caliber channels, and because they scrape through they cause more damage to themselves and to the vessel wall than in the larger caliber vessels. The sludged red blood cell is rough, the normal cell is smooth.[6] Also the number of functioning blood cells per cm would be influenced by the spacing of the masses and the anoxia would be influenced by this and by the rate of flow. Even an increased production of red blood cells would be of little avail because there is just so much space available between the masses of sludge. There is in a sense "standing room only."

The usual techniques of blood cell count, or differential count, because the solutions used dilute the blood and prevent coagulation and lyce or break up any agglutinates whether of sludge or fibrin clot may not reveal the number of cells put out of commission, or for that matter even the presence of sludge.

If hemoglobin is retained in the cells and its percentage lowered but little it still would not be readily available to the tissues. There would be a local anoxia in spite of good hemoglobin and color indices.

I wish particularly to call attention to the effect of even small strings of sludge on oxygen availability, and transfer:

2 cells stuck together smother 2 of the 4 surfaces; a loss of 50 per cent.

The apposition of two red blood corpuscles produces a surface contact for the apposed surfaces and an abnormal or changed functioning. Their cohesion has the effect of squeezing them together and hence diminishing their fluid content and deforming their structure. Two of their surfaces are smothered; these cells no longer function efficiently bilaterally or two-sidedly.

3 cells stuck together smother 4 of the 6 surfaces; a loss of 65 per cent.

4 cells stuck together smother 6 of the 8 surfaces; a loss of 75 per cent.

5 cells stuck together smother 8 of the 10 surfaces; a loss of 80 per cent.

10 cells stuck together smother 18 of the 20 surfaces; a loss of 90 per cent.

100 cells stuck together smother 198 of the 200 surfaces; a loss of 99 per cent.

Note that even 100 cells is not a large mass (it is less than 1/100,000 of a cu mm), yet it eliminates 98 of the surfaces of the 100 apposed cells and therefore to about the same extent the oxygen supply normally furnished by these cells when they are floating separately in the healthy blood stream, irrespective of any diminution in caliber of the vessels.

Remember that intravascular agglutinates may form rapidly, and dissolve rapidly, in which latter event they diminish oxygen exchange only temporarily, and it is not strange that they may be only transitorily observed or even entirely missed during the trigger episodes causing sudden symptoms and combinations of symptoms. Chronic intravascular coagulates, whether they deplete the cells of oxygen or prevent oxygen from reaching them, as do many poisons, the result is the same—an impairment of cell respiration from lack of energy. The body cells require their respiratory energy to preserve their structure and their function, so that if their respiration is sufficiently inhibited both structure and respiration disappear.[7]

To highlight the picture I call attention to the fact that the average adult human in his approximately 5 liters of blood has 35,000,000,000,000 blood cells equalling a total surface of about 3500 square meters. If placed side by side the cells would extend 163,000 miles, or nearly one-half the distance to the moon.

So take your space ship and wander along the bloody road; you might pick up some new ideas on the way, as for instance why and how sludge damages one organ and one part of an organ more than another, and what does sludging portend in youth and in aging people, and what can be done about it, and what besides the oxygen lack is occasioned and whether, where and when the whites and reds are segregated.

There is much, much more that I could tell you, much more that comes to mind because when one starts to investigate something interesting, no matter how simple, it is surprising how many new ideas crowd into the picture. But for the present these simple illustrations of how and to what extent intravascular agglutinates may cut down oxygen availability will suffice. This is a dramatic picture and admittedly a crude picture, but maybe like the early paintings of Grandma Moses, it will arouse your interest. I exhibit it for your viewing.

NOTE: The electronmicrographs were all obtained from Doctor Edward H. Bloch, Western Reserve University.

140 EAST 54TH STREET

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The Scientific Papers of the American Broncho-Esoghagological Association

XLIII

THE EFFECT OF THE BARBITURATES ON LARYNGEAL FUNCTION

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AND

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HANOVER, N. H.

This is a report of changes in laryngeal function which follow administration of the commonly used barbiturates. These changes are recorded in electromyograms from the vocal cord, the cricothyroid muscle, and the posterior cricoarytenoid muscles of animals along with records of respiration, and in many experiments, electrocardiograms. In this way we have endeavored to evaluate any basic changes which might occur in the larynx as a consequence of the use of various barbiturates in clinical anesthesia.

METHOD

Goats were used as experimental animals. Basic anesthesia was an initial dose of pentobarbital sodium given intraperitoneally, 0.45 gm per kilo, followed by intravenous drip of pentobarbital Na 0.6 per cent. This is a very dilute solution and serves only to maintain a basal anesthesia. Our method varies from that previously reported,[2] in that in these experiments we have added an electrode in the vocal cord. This was done by section of the thyroid cartilage in its mid-portion anteriorly (similar to the procedure in laryngo-fissure). The posterior cricoarytenoid muscle was exposed by elevation of the cricoid cartilage following section between it and the first tracheal ring. In previous experiments we made no record of vocal cord electromyograms. In some few experiments we exposed the posterior cricoarytenoid muscles through a window in the posterior larynx. We have improved our method of recording respiration by the use of a thermistor in place of the pneumograph and microphone.[2] The thermistor is a heat sensitive

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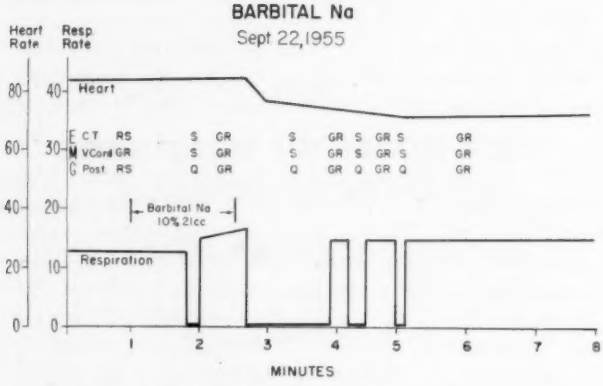

Fig. 1.—Diagram of changes produced by barbital sodium.

resistor which responds rapidly to changes in temperature. It was placed in the lumen of the tracheal cannula. The changes in resistance due to the cooling of the thermistor by the inspiratory and expiratory air stream were recorded. It was felt that this gave us the best indication in time that we have had to date, particularly for inspiration. In all other particulars our method is similar to that previously reported. The various barbiturates were injected intravenously in varying amounts at various rates.

EXPERIMENTAL RESULTS

Barbital Sodium (Veronal Sodium). This material was injected 11 times in 3 experimental animals. All experiments are the more recent ones(with an electrode placed in one of the vocal cords as well as in the cricothyroid and the posticus). In this particular preparation with the electrode in the vocal cord, we have actually one of the circumstances which might produce spasm. In all the results were essentially the same. Unless we injected a sufficient amount of the drug at a rapid rate sufficient to produce a cessation of respiration there were no striking changes. If respiration was stopped, a very interesting cycle developed. The experiment of September 22, 1955 may be taken as an example. Figure 1 shows graphically what took place during one typical episode. Recorded are the heart rate, respiratory rate and the injection of the barbital sodium. A brief description of the electromyogram is distributed at appropriate intervals. CT indicates cricothyroid muscle, VC indicates vocal cord,

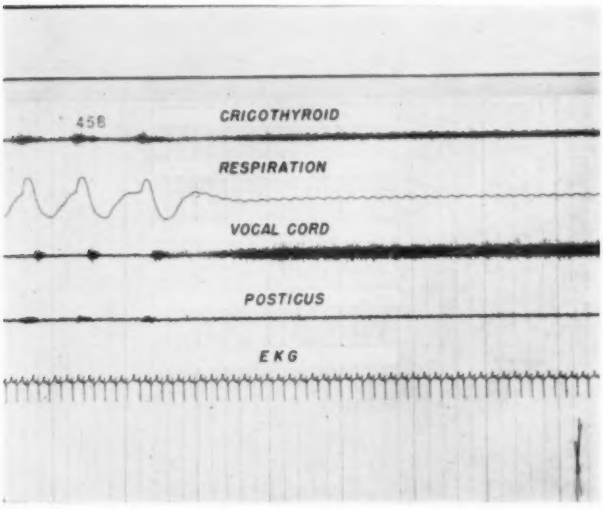

Fig. 2.—Electromyographic record from laryngeal muscles at end of injection of barbital sodium. Ventilation and electrocardiogram also shown.

Post indicates posterior cricoarytenoidius muscle. The symbol R is used to indicate rhythm, S for spasm, and Q for quiescence and GR indicates good rhythm. The combination RS indicates rhythm superimposed on spastic background. A photograph of the electromyograph record centered on the end of the barbital injection is shown in Figure 2.

We injected 21 cc of 10 per cent barbital sodium over the period of 108 seconds. Before the injections respiration was 14 and the heart rate was 84 per minute. When 11 cc had been injected respiration stopped transiently. The background rhythm of the CT diminished; the VC showed a sustained background activity during the apnea. The background activity of the posticus diminished. After 12 seconds of apnea the respiration resumed while the injection was continued slowly. The respiratory rate was transiently between 15 and 17 and 12 seconds after the end of the injection, respiration again stopped. For about one and one-half minutes brief intermittent respiratory activity developed again. Always during ventilation there was good respiratory rhythm in the EMG's. During the apnea periods, the posticus was quiescent and the two adductor muscles showed increased activity or spasm. The heart rate changed very

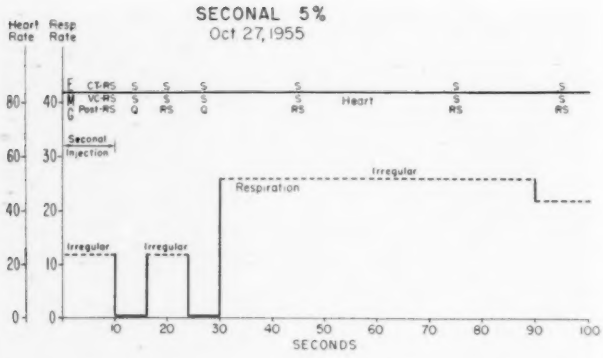

Fig. 3.—Diagram of changes produced by secobarbital (seconal).

little and eight minutes after the beginning of the injection it had dropped to 72 per minute. During periods of ventilation, the respiratory rate remained at 15 per minute.

Secobarbital (Seconal). Seconal, an ultra rapid barbiturate, was injected intravenously 14 times in 4 experimental animals. Typical is the experiment of October 27, 1955 in which 2 cc of 5 per cent seconal was injected over a period of 10 seconds (Fig. 3). Respiration is 12 min and heart rate 84/min prior to injection. Respiration becomes irregular and is slowed, complete cessation develops immediately following the injection for a period of approximately six seconds. It is followed by irregular inspiratory and expiratory cycles for eight seconds, again followed by cessation of respiration for about six seconds, then follows a pattern of irregular respiration (without apnea) at no time returning to the regularity which existed prior to the injection. The heart rate, 85, remains the same, the normal rhythm existing in the cricothyroid muscle and in the vocal cord is eliminated. A pronounced spasm develops during respiration. This followed during apnea by a decrease in amplitude. The EMG in the posticus is quiet when respiration stops (Fig. 4). When the dose of seconal is doubled, that is, 4 cc over a period of 35 seconds, spasm increases in the CT and the V.C and the posticus is quiescent. The heart rate remains constant. In some experiments, where spasm existed in all three muscles, prior to the injection of the large amount of seconal (18 cc over a period of 90 seconds) the amplitude of spasm in the cricothyroid muscle decreased, the vocal cord became quiescent and spasm increased in the posticus. In other experiments, persistent

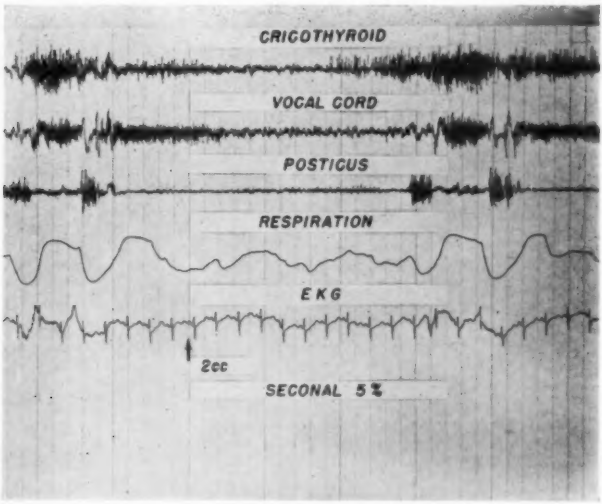

Fig. 4.—Electromyograms, ventilation, and EKG after secobarbital (seconal). Experiment of October 27, 1955.

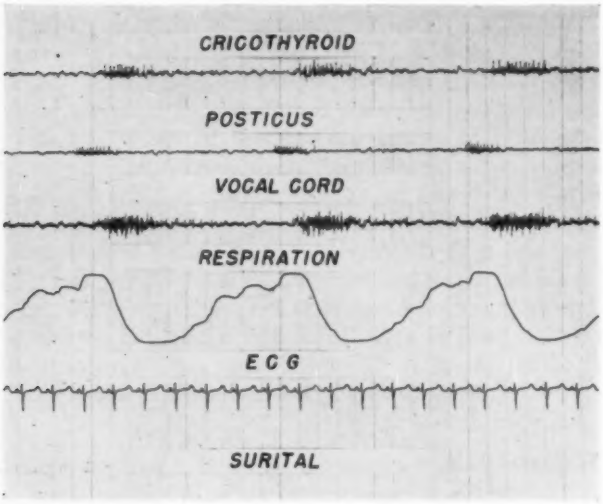

Fig. 5.—Record of electromyogram, ventilation, and EKG before thioamylal (surital). Experiment of November 3, 1955.

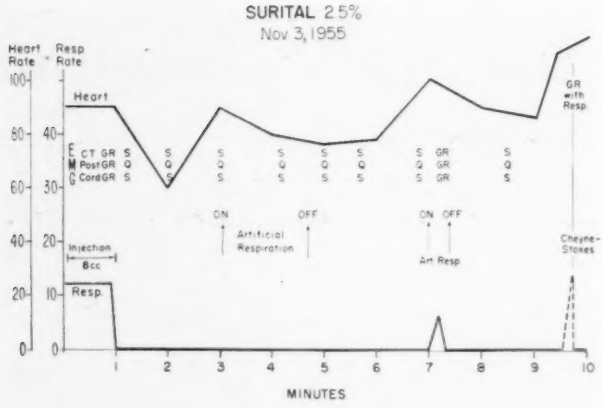

Fig. 6.—Diagram of changes produced by thioamylal (surital).

spasm continued unabated in all three muscles following large doses of seconal. It must be remembered that in all these experiments there was an electrode in the vocal cord.

Thiamylal (Surital). This drug was injected 10 times in 4 experimental animals. In one experiment we injected 8 cc of 2.5 per cent surital in 54 seconds. Prior to the injection, normal rhythm existed in all 3 muscles (Fig. 5). The respiratory rate was 12 per minute and the heart rate was 90 per minute (Fig. 6). Immediately following injection respiration ceased (Fig. 7), the normal rhythm of the cricothyroid muscle was replaced by spasm and the posticus became quiet and a pronounced spasm developed in the vocal cord. The heart rate slowed to 60 per minute and the respiration had stopped. At the end of six minutes, the heart rate had increased to 78 per minute and with the development of anoxea seven minutes after injection the heart rate had increased to 100. During the ninth minute following injection, Cheynes Stokes respiration developed and the heart rate increased to 112. From 9½ minutes to 53 minutes after the end of the injection, Cheynes Stokes respiration continued and the heart rate returned to 90 which was the initial rate (Fig. 5). The animal was then destroyed.

Thiopental Sodium (Sodium Pentothal). Sodium pentothal was injected 22 times in 9 experimental animals. In an experiment on May 14, 1955 (Fig. 8), we injected intravenously 19 cc of sodium pentothal into an animal whose weight was 20 kilos over a period of

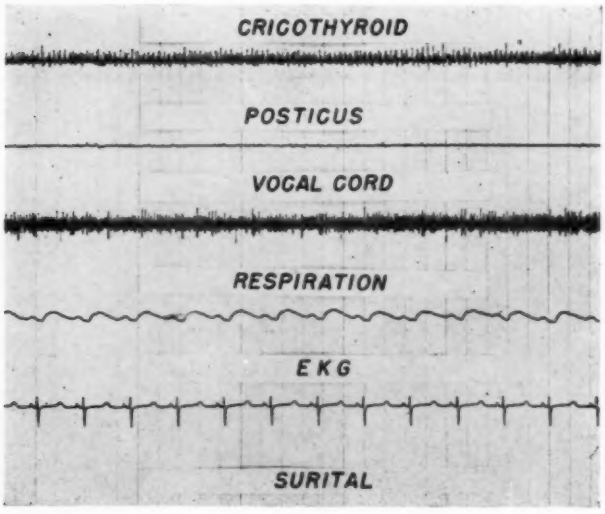

Fig. 7.—Apnoea and spasm following thioamylal (surital). Experiment of November 3, 1955.

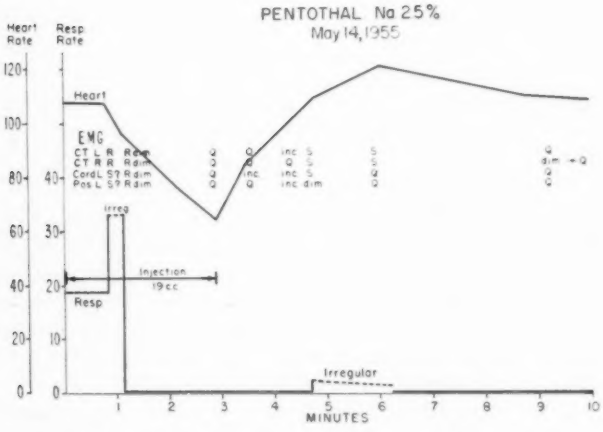

Fig. 8.—Diagram of changes following pentothal sodium.

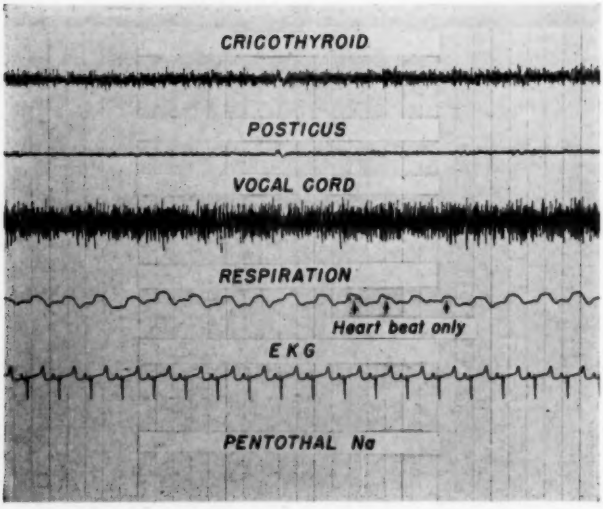

Fig. 9.—Experiment of November 10, 1955, showing apnoea and spasm following pentothal sodium 9 cc of 2.5 per cent.

two minutes and 53 seconds. Prior to injection of the drug, respiration was 18 per minute and the heart rate was 108 per minute. After 6 cc of sodium pentothal was injected respiration became irregular and increased to approximately 36 per minute. When 8 cc had been injected respirations stopped. (This occurred at 70 seconds after the beginning of injection.) When 11 cc of sodium pentothal had been injected intravenously the heart rate had slowed slightly to 106 and the electromyogram in the cricothyroid muscle had lost its rhythm and its frequency had decreased. Its amplitude also was less. The electromyogram of the vocal cord likewise evidenced a diminution in amplitude and frequency, and the heart rate slowed to about 96 per minute. When the 19 cc had been injected completely, apnea continued, the heart rate slowed considerably to 64. Electromyograms of the cricothyroid muscle was quiescent and the electromyogram of the vocal cord and the posticus muscles showed greatly decreased amplitude and frequency. Twenty-five seconds later the amplitude and frequency of the EMG of the vocal cord increased. That of the cricothyroid both on the right and left side remained quiet, the posticus was quiet. This situation was maintained for about 105 seconds. The apnea persisted and when respiration again was resumed

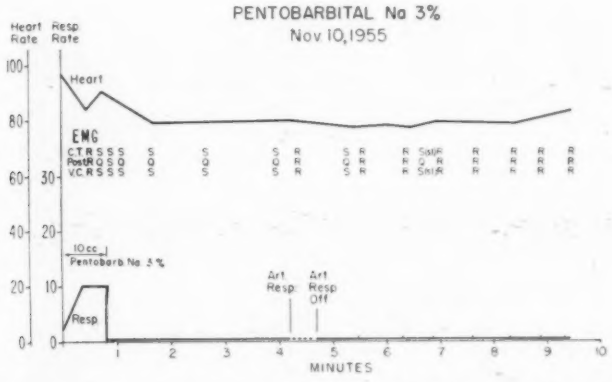

Fig. 10.—Diagram of changes following pentobarbital sodium 3 per cent.

at a very slow rate of about four per minute, spasm developed in the electromyograms of the vocal cord, the cricothyroid and to a lesser extent in the posticus muscle. The heart rate returned to that which existed prior to the injection (108 per minute).

In another experiment on November 10, 1955, we injected 9 cc of a 2½ per cent solution of sodium pentothal in 50 seconds. Prior to the injection, there had been a moderate amount of spasm in the cricothyroid, the posticus and the vocal cord. When 7 cc of the drug has been injected, the posticus became quiescent, the vocal cord and the cricothyroid muscle went into spasm (Fig. 9). Within 10 seconds respiration had stopped completely, the heart rate remained about the same. At the end of three and one-half minutes following a brief period of artificial respiration, the posticus showed continuous background activity of mild spasm with activity in all three muscles gradually increasing. Approximately three minutes following the injection, the spasm diminished very markedly and continued for about seven minutes when the animal took a single breath. This breath set up a respiratory rhythm in muscles for a single cycle. The animal continued to breath irregularly at intervals of 20 to 40 seconds for about 12 minutes. Activity in all three muscles then gradually increased.

Pentobarbital Sodium (Nembutal). This drug was given a total of 10 times in 7 different animals. In an experiment of November 10, 1955, we injected 10 cc of 3 per cent pentobarbital sodium over a period of 50 seconds (Fig. 10). Heart rate prior to injection

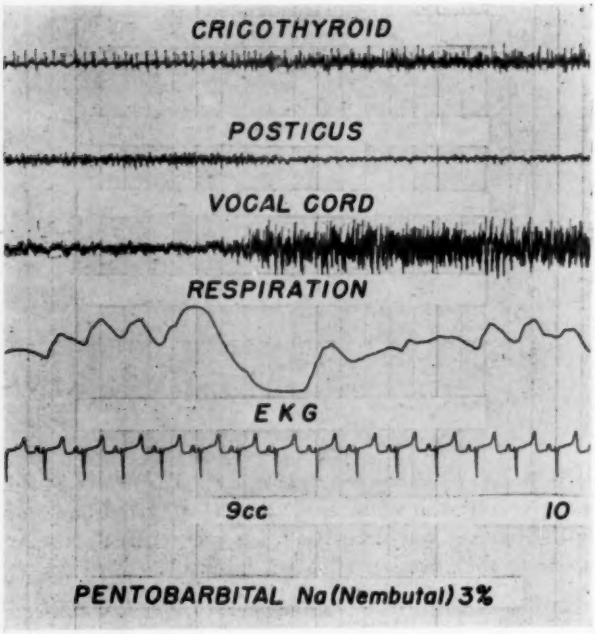

Fig. 11.—Changes during injection of pentobarbital (nembutal) sodium. Experiment of November 10, 1955.

was 96 per minute. Respiration is irregular and from one to three per minute. During the period when the pentobarbital sodium was being injected, the heart rate was 84 per minute. At the end of the injection, it increased to 90 per minute. Respiration stopped when 10 cc had been injected. No rhythm existed in any of the muscles but there was minimal spasm present in all three. When 9 cc of the pentobarbital sodium had been injected, the cricothyroid and the vocal cord showed spasm. The posticus becomes quiescent (Fig. 11). This continued for 210 seconds when a slight respiratory effort was made during a period when artificial respiration had been utilized for about 30 seconds. Then there was no spontaneous respiratory effort for another 48 seconds but the EMG's of the C.T and V.C gradually diminished. The posticus is quiescent until a single normal respiratory effort was made 84 seconds after the first recorded respiration. Here, relatively normal reciprocal relationships were shown (Fig. 12). Single respiratory efforts were made at intervals of from

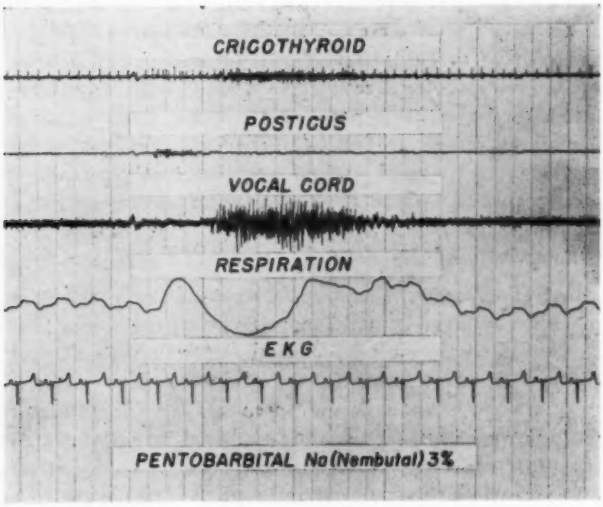

Fig. 12.—Reciprocal inhibition during a single respiratory effort after a

18 to 46 seconds. Normal respiratory rhythm was exhibited during each respiratory cyle and between the respiratory efforts there was a moderate background firing in the cricothyroid and the vocal cord. Toward the end of this interval, small background potentials began to appear in the posticus. During the next 5 minutes the background activity of the C.T and posticus increased. This record suggests a mild spasm in these muscles.

In another experiment of May 17, 1955, we injected 10 cc of pentobarbital sodium in 12 seconds. Prior to this injection, the respiratory rate was 21 per minute, the cricothyroid and the vocal cord had good respiratory rhythm. Respiration stopped 18 seconds after the end of the injection and all EMG's diminished markedly in rate and amplitude. 30 seconds after respiration stopped all muscle action potentials disappeared and remained so for 90 seconds. They then reappeared in the cricothyroid and the vocal cord, but showed moderate spasm. The posticus was not completely quiescent but minute action potentials reappeared at the same time in the other muscles. About every minute there occurred a gasping respiration accompanied by a burst of electrical activity in all three muscles. This continued for about four minutes and then all activities except the pneumocardiogram disappeared.

COMMENT

These experiments have been carried on for approximately three years. The earlier ones were reported in January 1954.[2] At that time we considered that experimental laryngospasm and probably any laryngospasm was produced reflexly by stimulation of sensory nerves leading from the laryngeal region. We felt that if the depth of anesthesia is inadequate the accumulation of secretion was sufficient to precipitate laryngeal spasm. When precautions were taken to keep the larynx clean and as free as possible from all irritants the use of pentothal and pentobarbital in full anesthetic (adequate or even overdosage) the activity of the intrinsic musculature was diminished.

In these experiments, there was always an electrode in the vocal cord and this may have caused some of the spasm observed. When apnea developed, as a result of central depression (a clinical overdosage) the electromyograms of the abductor (the posticus) frequently became quiescent and the potentials for the adductors continued to indicate spasm. This could be based on respiratory reflexes similar to those reported by Green and Neal[1] who found that the normal activity of the abductor muscles of the larynx present during inspiration (recorded electromyographically) was abolished by artificial inflation of the lungs. The electrical activity manifest during expiration in the adductor muscles (the cricothyroid and the vocal cord) is on the other hand accentuated by artificial inflation of the lungs.

Thus for the first time particularly using the thiobarbiturates we have observed a laryngospasm possibly based on central (medullary) depression. Tovell et al.[3] have made a statistical analysis of the effect of thiobarbiturates on the human. It must always be remembered that these animals were kept under anesthesia. The experimental drugs were added. Care was taken to see that the basal anesthetic was at a minimum. These experiments probably should be repeated in part at least using a decerebrate preparation.

CONCLUSION

We have no evidence that a moderate dose of any of the barbiturates even in the presence of an irritant in the vocal cord makes the animal more susceptible to laryngospasm.

If the dose of barbiturate is great enough to cause apnea, we have striking evidence of hyperactivity of the adductors and inactivity of the abductors at all times except when an inspiratory effort is made. Artificial respiration carried out with very moderate pressures did not elicit the dramatic responses which were present during the inspiratory effort. (This requires further investigation.)

The quick acting thiobarbiturates (thiopental and thiamylal) increased the electrical activity of the adductors of the larynx more than the other three barbiturates examined. The thiobarbiturates act more promptly to produce apnea by central nervous system depression and have caused the greatest adductor spasm. If they are given slowly enough, and in small enough quantities their action resembles that of the other barbiturates.

We have the impression that barbital sodium produces less central nervous system depression than the other barbiturates we considered, but this may be due to the brevity of our experiments.

HITCHCOCK CLINIC

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XLIV

BRONCHOSCOPY IN THE TREATMENT OF SEVERE ACUTE BRONCHIOLITIS IN CHILDREN

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(By Invitation)

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Acute bronchiolitis is a clinical syndrome most commonly seen in young infants. The signs and symptoms are primarily due to obstruction of the infant's tiny bronchioles by inflammatory edema of the mucosa, sticky, tenacious secretions within the lumen and a superimposed element of bronchospasm. The resultant partial obstruction leads to poor air entry and obstructive emphysema. Areas of collapse may occur if bronchiolar obstruction becomes complete. Death may result from anoxemia or pulmonale.

The primary problem is that of obstruction of the air passages and many methods have been advocated to alleviate this obstruction. Agents to liquefy the tenacious secretions, adrenalin and ACTH to relieve bronchiolar spasm and minimize inflammatory edema, moist air, intravenous fluids, etc., all play important parts in the management, but are sometimes of no avail.

It is the purpose of this paper to discuss the role of bronchoscopic aspiration, as a life saving measure in patients not responding to the above therapy.

Etiology is essentially unknown, and throat cultures usually yield normal respiratory flora. On occasions the pneumococcus, streptococcus, staphylococcus and H.Influenza are grown, but these may well be secondary invaders. Several observers feel that this condition is the infantile counterpart of primary atypical pneumonia, but cold agglutinin titres have not been elevated. Viral studies have not as yet been productive.

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The basic process is inflammation of the entire thickness of the bronchiolar walls, with spread of the reaction to the interstitial tissues and to the alveoli, so that there is, in addition, an interstitial pneumonitis.

The majority of the patients are less than six months of age, but the condition is not uncommonly seen in older infants and young children.

Frequently the infant has a slight cold for two to three days, but does not appear particularly ill. Dyspnea then supervenes, either gradually or suddenly. The respirations become rapid, shallow and labored, usually with an audible expiratory wheeze and prolongation of the expiratory phase. Inspiratory difficulty is usually evidenced by indrawing of the suprasternal notch and intercostal spaces. There is a constant, ineffectual, expiratory cough. Pallor, cyanosis and restlessness, with constant whimpering testify to the anoxia. Convulsions, due to cerebral anoxia may occur. Fever is variable.

Physical examination reveals an emphysematous chest with a hyperresonant percussion note. The diaphragms are depressed so that the liver may appear enlarged. Air exchange is poor and the expiratory phase prolonged, wheezy and difficult. Inspiration is also difficult and air entry may occur only at the end of the inspiratory effort. Every type of rale and rhonchus may be heard at this time. Heart sounds are distant and rapid but the heart may slow terminally.

All of the infant's energy is used for respiration and attempts to feed are feeble. Air hunger results in marked restlessness. Usually the pharynx is reddened and contains a great deal of tenacious mucus which the infant is unable to swallow.

In the younger infants various types of congenital heart disease, especially endocardial fibro-elastosis, large septal defects, vascular rings, etc., must be ruled out, and in older infants and children the possibility of a foreign body, or asthma should be considered. Asthmatic bronchitis occurs in older children and is not nearly so severe as bronchiolitis.

The white blood count may be normal or moderately elevated and the differential count is usually normal. Chest x-ray shows the picture of emphysema but may show heavy bronchovascular markings, peribronchial infiltration and even areas of collapse and consolidation.

Treatment is aimed at controlling the infection and relieving bronchiolar and bronchial obstruction. The response to antibiotics is not dramatic and it is probable that they do nothing to the primary

etiological agent but merely prevent or control secondary invaders. It is the custom here to use penicillin and streptomycin but occasionally broad spectrum antibiotics are used intravenously.

The main problem then is the relief of respiratory obstruction. As mentioned above, this obstruction is due to three factors—inflammatory edema of the bronchiolar wall, tenacious secretions in the air passages and spasm of the bronchial musculature. Walker has clearly defined the role of ACTH and cortisone in relieving the inflammatory edema and bronchospasm and certainly in many of our cases the administration of these agents has produced dramatic results.

The following routine is used at the Hospital for Sick Children, Toronto. On admission the patient is given a therapeutic trial of adrenalin 2 mm in the admitting department and if this has a beneficial effect, it may be repeated at two to four hour intervals. The infant is then placed in a croupette with as much humidity as possible. One-half of one per cent ephedrine nose drops are instilled in the nose and an antibiotic administered. Of the utmost importance is frequent suctioning of the nasopharynx to assist the baby in getting rid of the tenacious secretions. This is repeated every 15 to 30 minutes and the baby's position is changed frequently. In severe cases an intravenous injection of 5 per cent glucose in distilled water is started to obviate the necessity of oral feedings which tire the baby unduly. If started, it is used also as the route for administration of antibiotics. The rate is maintained between 20 - 30 cc per hour to prevent overloading of the already struggling cardiovascular system. Intravenous cortef or ACTH is given in appropriate doses depending on the age and weight of the baby. Ten to 15 mgm of ATCH in 250 cc 5 per cent glucose in distilled water and administered intravenously over an eight hour period will cause maximal adrenal stimulation. Cortef is used in the most severe cases, 10 - 20 mg at four hourly intervals.

Blood is given very slowly in amounts of 5 cc/lb. only if the Hgb. is below 9 gm per cent. Digitalis is used if there is evidence of congestive heart failure.

Syrup of hydriotic acid or saturated potassium iodide is sometimes used to help liquefy the secretions. Aminophylline is usually not well tolerated by small infants.

On this regimen most of the patients do well. Occasionally, however, an infant becomes progressively more exhausted and the respiratory efforts more feeble. Air exchange is practically nil and mottled cyanosis appears. The baby may convulse from cerebral anoxia. On other occasions, infants are admitted in this condition and it is obvious that death will occur in a matter of minutes if some-

thing heroic is not resorted to. It seems logical that the thing to do is to clear the air passages as quickly and completely as possible. Certainly there is no time for a trial on the above regimen. Under these circumstances the patients have been bronchoscoped as an emergency procedure and the results have been very gratifying.

EXPERIENCE WITH BRONCHIOLITIS

In the eight year period 1948-1955 (1955 figures not complete) 900 patients with bronchiolitis have been admitted to the Hospital for Sick Children, Toronto, 173 in the years 1948-1951, and 727 since 1951. There has been a marked increase during the past two years with 268 cases occurring in 1954 and 215 in 1955 (incomplete).

Many mild cases seen in the out-patients' department have been treated at home.

Most of the cases have responded to medical treatment.

Since 1952, bronchoscopic aspiration has been considered to be an important part of the management of the severe case, and has been carried out in 33 of 727 patients with bronchiolitis.

We have had difficulty in establishing strict criteria for bronchoscopic aspiration in these cases. As mentioned above there is no difficulty in reaching the decision in the group of patients admitted in a moribund condition, cyanosed and gasping. Also there is no problem in the group of patients, who after a variable period of medical therapy ranging from several hours to five days, suddenly "go flat" and would almost certainly die in a matter of minutes if something were not done. More difficult are the patients who appear to be getting progressively worse after several hours of medical therapy. In this group we have been guided by the age of the patient, the general physical condition, pulse and respiratory rate, presence of cyanosis and cirumoral pallor, air hunger as evidenced by restlessness, sleeplessness and incessant whimpering, and degree of tiredness as judged by the force of the respiratory movements, sucking ability, etc.

Fifteen patients were bronchoscoped within the first few hours after admission because their general condition appeared to be deteriorating rapidly despite ordinarily adequate medical therapy. Seven patients were bronschoscoped as a "life or death" procedure, these having suddenly collapsed one or more days after admission. It is impossible to predict when a patient in the first group will suddenly become one of this group. Four patients gradually deteriorated over a few days, and although not desperately ill, were felt to have a more favorable outlook if the procedure were carried out.

One patient was bronchoscoped on admission because of her condition, one because of slow response to conservative therapy after several days, two because of a suspicious history of having aspirated either a feeding or a foreign body, and three because of their poor general condition plus the fact that there was collapse of a lobe.

FINDINGS AT BRONCHOSCOPY

Bronchoscopy in these patients is rarely an elective procedure but rather a sudden emergency at which time the patient is in marked respiratory distress and in a state of collapse. Under these circumstances there is no question of using an anesthetic to introduce the bronchoscope.

The bronchoscope (usually a 3½ mm x 30 cm) must be introduced quickly and accurately into the trachea. Any appreciable delay in passing the bronchoscope into the trachea after the laryngoscope has been introduced into the laryngopharynx can very well precipitate death in the cases which are already almost terminal. The mistake of passing the bronchoscope into the esophagus must be avoided or, at least, the error must be rectified quickly. In this respect particularly, one must be sure of having the bronchoscope in the tracheobronchial tree before connecting the oxygen. Inflation of the stomach with oxygen will only add to the patient's difficulty.

When the bronchoscope is first introduced into the trachea, secretion obscures one's vision and aspiration of the secretion must be carried out quickly. Invariably this secretion is very viscous, tenacious and of a greenish color. In the collecting bottle it seems almost semisolid in consistency. Usually it is necessary to run water through the aspirating tube in order to bring the thick exudate into the collector.

Once the trachea and bronchi can be seen, marked bronchospasm is usually evident. The mucosa of the tracheobronchial tree is inflamed and swollen to a variable degree throughout.

When the bronchospasm is severe and the air entry in the chest has not improved appreciably, it has been found that by the administration of an ether-oxygen mixture via the bronchoscope the bronchi gradually relax and the air entry in the chest improves as indicated by auscultation. This enables the bronchoscopist to aspirate more distally in the bronchial tree. Furthermore the ether seems to promote serous secretion and thus makes the exudate less viscid. The bronchospasm will disappear entirely when the patient is sufficiently anesthetized although it will reappear as the anesthetic is lightened. In spite of the return of the bronchospasm the air entry remains improved,

the patient's color is much better than pre-operatively, and the pulse rate is lower. It must be pointed out that the improvement in the patient's condition is not as dramatic and as sudden as one sees after a tracheotomy has been performed for obstructive laryngeal lesion, but nevertheless in nearly all the cases in this series the procedure has been very definitely a life saving measure.

Of the 33 patients in this series who were bronchoscoped, bronchoscopy had to be repeated on three of the patients in whom the same clinical picture recurred in 24 to 48 hours but again improvement occurred with the patients going on to complete recovery. There were no deaths among the cases of primary acute bronchiolitis that were bronchoscoped. One patient was tracheotomized because of the severity of the illness and because improvement did not immediately manifest itself by bronchoscopy alone. This patient made an excellent recovery.

The cases of bronchiolitis that were treated by bronchoscopy and reported in this series were those selected as being typical bronchiolitis as defined in the opening paragraph. Those patients who had other diseases (with bronchiolitis as a complication) such as fibrocystic disease, congenital heart disease, aspiration of foreign material, or asthma, have not been included. Nevertheless, similar results were obtained by bronchoscopy in many of these cases as well.

One may wonder how bronchoscopy could be of significant value in this disease when the pathology is primarily in the bronchioles which obviously cannot be reached with a bronchoscopic aspirator. It is our belief that the thick exudate accumulates in the major bronchi and trachea, gradually occluding these structures, and therefore increasing the effort of the patient to effect pulmonary ventilation, and overtaxing an already overburdened cardiopulmonary system. This secretion is too thick and tenacious to be coughed out by the acutely ill and weakened infant. Aspiration of this material eliminates one factor contributing to the infant's distress. Moreover, oxygen is administered in a high concentration which in itself is at least a temporary adjunct in the therapy. The value of anesthetizing the child with ether may be debatable although it has appeared to us to make the bronchoscopy more effective. In one case in particular, the use of ether in relieving the bronchospasm appeared to be a very deciding factor in the infant's recovery. Only when this infant was anesthetized did the heart rate and air entry improve and this interval enabled treatment with neocortef to take effect.

On examining the x-rays of these patients with bronchiolitis before bronchoscopy has been performed, we have been impressed by

the number who have shown radiological evidence of atelectasis of the right upper lobe, along with the picture of emphysema which is considered to be typical in bronchiolitis. This finding would tend to support the idea that the thick secretion accumulates in the trachea and main bronchi, rather than the more distal bronchi. Otherwise, one would expect atelectasis of the lower lobes before, or instead of, the right upper lobe. X-rays after bronchoscopy indicate that the atelectatic lung has almost invariably expanded.

REPORT OF CASES

CASE 1. R.B., aged four months. Five days prior to admission this infant developed a slight cough and cold. Three days before admission he was slightly feverish and the following day was noticed to be wheezy and slightly dyspneic. On admission he was found to be quite well developed and nourished. Temperature was 104, pulse 138, and respirations 60. He was moderately dyspneic with prolonged wheezy, expirations, suprasternal and intercostal indrawing on inspiration with fine inspiratory rales heard generally, and evidence of obstructive emphysema. Hgb. was 10.2 gm, W.B.C. 8,500 with a normal smear and differential. Chest x-ray showed only emphysema. He was treated in a croupette with moisture and oxygen. Penicillin and streptomycin were given every four hours. The nasopharynx was suctioned frequently and yielded thick tenacious secretion.

On this regimen he appeared to improve and the following morning his temperature was normal. Throat culture grew only "usual flora." However, he still had a troublesome expiratory cough and wheeze and indrawing as above. His color was slightly dusky when taken off of oxygen. Suddenly, 24 hours after admission, he became deeply cyanosed. His eyes rolled up and he began to have convulsive jerks of his limbs. Respirations were gasping and infrequent. He was picked up and rushed to the operating room where a bronchoscope was passed within four or five minutes of his collapse. Respirations immediately improved. The tracheobronchial mucosa was generally red and swollen. Tenacious mucopus was aspirated. He was slightly but definitely improved by the procedure. ACTH was then administered intravenously. During the next 24 hours he gradually improved and appeared to be out of danger after about 36 hours.

CASE 2. B.B., aged four months. This baby developed a slight cough and cold four days before admission and the following day became wheezy. Six hours before admission he developed marked respiratory distress and fever. On admission he appeared extremely ill and was moderately cyanotic. The pharynx was injected and was filled

with thick mucus. Respirations were rapid and shallow with generalized coarse inspiratory rales and prolonged, wheezy expirations. Hgb. was 10 gm, W.B.C. 20,000. Chest x-ray revealed generalized emphysema, heavy bronchovascular markings and slight infiltration of the right upper lobe. He was treated with oxygen in a croupette, penicillin and streptomycin, intravenous fluids, intravenous ACTH and adrenalin. Despite this there was no improvement after 4 to 5 hours and it was felt that he could not continue for much longer in his present condition.

Bronchoscopic aspiration was performed. The bronchial mucosa was generally inflamed and thickened and a great deal of thick mucoid secretion was removed. There was immediate improvement. Postoperatively he improved gradually over a four day period. A light growth of pneumococcus was cultured.

In this case, it would seem that bronchoscopic aspiration tided him over the critical period, allowing the other therapeutic agents to take effect.

CASE 3. P.O., aged two months, a white male, was admitted on February 28, 1956. Five days before admission he became irritable and began to refuse feedings. Three days before admission be began to cough. Symptoms became progressively worse and he became dyspneic and cyanotic.

On admission he appeared extremely ill and had a barking expiratory cough and grunt. Fine inspiratory rales could be heard everywhere but there was no prolongation of the expiratory phase and no evidence of bronchospasm. Air exchange was very poor and he remained cyanosed even in oxygen. The cardiac rate was just 60/minute and in view of the fact that this infant had had blue spells during the first few weeks of life, some form of congenital heart disease with failure was suspected. Temperature was normal, Hgb. 11.5 gm, W.B.C. 12.8 with a normal smear and differential. Chest x-ray showed a small heart, emphysema, and minimal pneumonitis in the right upper lobe.

Despite therapy with oxygen, croupette, frequent aspiration of the nasopharynx, I.V. fluids, penicillin and chloromycetin, he continued to deteriorate.

Seven hours after admission it was decided that his only hope lay in the possibility that there was obstruction in the air passages which could be relieved. Consequently a bronchoscopic aspiration was performed. A 3½ x 30 scope was passed into the trachea and this was found to contain very thick secretion. However, a surprise

finding was a very marked spasm of the entire tracheobronchial tree, as there was still no clinical evidence of such.

An ether anesthetic was given and eventually the spasm disappeared. As it did, the heart rate speeded up to about 110/minute and the cyanosis disappeared. More secretion was removed.

However, as soon as the anesthetic lightened, the spasm returned and it was felt that the baby would likely die if the scope were removed. Adrenalin 2 mm was given, followed by I.V. cortef and the bronchoscope was kept in place until the spasm released.

During the next two days there was a gradual improvement, although considerable cortef and adrenalin were necessary. Complete recovery ensued in ten days.

In retrospect, it would appear that the misleading sign of a slow heart rate was due to terminal anoxia of the cardiac muscle or cardiac center in the brain, and the absence of the usual signs of partial bronchiolar obstruction was due to the fact that the infant was completely unable to make effective respiratory efforts.

CONCLUSIONS

It is our feeling that many of the patients who were bronchoscoped would certainly have died if the procedure had not been carried out. Because of the marked variability of the clinical course, we are unable to state whether or not the duration of symptoms has been in any way affected. We hope that with more clinical experience we shall be able to draw up more definite criteria, by which to decide which patients should have bronchoscopic aspiration.

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XLV

THE OPEN-DOOR POLICY IN ENDOSCOPY

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SYRACUSE, N. Y.

Frequently, two previously unrelated subjects will become closely connected in our thoughts. New insights are quickly seized upon and we feel that we have grown. We sense a broader, more mature viewpoint. Our decisions are less dogmatic and more circumspect. Two such subjects are the "open door" policy and the field of endoscopy.

Secretary of State John Hay initiated the open door policy in China in 1899 as America's free enterprise answer to the large group of European nations each of which not only wished to monopolize industrial trade but to actually partition China. Mr. Hay hoped that these countries together with the United States could join in helping China regain its independence and reform its government. Unfortunately, internal politics in the rapidly changing Chinese scene led to the Boxer Rebellion. Only the passing of the Dowager Empress who, shrewd and calculating as she was, clung to the status quo and refused to recognize the changes wrought in her nation by close European and Western contact, finally opened the path. Perhaps the greatest need was a far-seeing domestic and foreign policy.

As a field, endoscopy long since "opened the door." It has stimulated other branches of the medical profession in the indications for and the technique of endoscopy. We are greatly pleased at the breadth of our field, but we are frequently puzzled at the intricate inter-relationships which have developed.

The majority of us do not limit our practices to bronchoesophagology. We rely on otolaryngology for the bulk but have a special interest in problems of the tracheo-bronchial tree and esophagus.

Depth perception with monocular vision and a facility with a variety of unusual instruments requiring dexterity have been our major assets in exploring the lower respiratory and upper alimentary tracts.

Many have eagerly shared their enthusiasm with us and the scientific articles telling of our advances are read not only by the chosen few with otolaryngological training, but by all who wish to share our interest. What has our domestic and our foreign policy been?

Since the majority of our changes are stimulated by outside influences, let us look at our foreign policy first.

Today, the medical profession has many anesthetists trained in endotracheal intubation, many thoracic surgeons trained in bronchoscopy and esophagoscopy, gastroenterologists trained in gastroscopy; general surgeons and proctologists trained in sigmoidoscopy.

We still feel a certain consternation when our colleagues in general practice and internal medicine refer patients for diagnostic bronchoscopy or esophagoscopy to the thoracic surgeon rather than to the otolaryngologically trained bronchoesophagologist. Or, when the same colleagues request from us a laryngeal examination after the thoracic surgeon has already performed an endoscopy and come up with normal findings with the patient still coughing and hoarse.

The status quo has been altered and seemingly, at the moment, to our professional disadvantage. Are we, therefore, not justified in making every effort to hold on to this part of our practices insisting that when any such procedure is done that it be done by a member of the ear, nose, and throat service? If we open the door, will that portion of our practices go out the door? Trying to look at the broad picture when a definite part of our livelihood is so jeopardized makes it difficult to be objective and to evaluate properly. As ethical practitioners, wherein do our loyalties lie?

Conscious recognition of conflicts in loyalties, especially when more than two such loyalties are involved, is one of the signs of maturity. It, also, reminds us that the man on the heights faces problems of which the man in the valley never dreamed. Truly our first loyalty is to the patient. Our second is continually to maintain a high standard of medical practice. Thirdly, it is our privilege to impart by precept and specific instruction our developed abilities to younger physicians. And fourthly, we wish to maintain our loyalty to our specialty—endoscopy. Let us look more closely at each of these four. Then we shall relate them to a local situation so that each of us may compare with our own practices both present and future.

Of course, our first concern is our patient. It is our responsibility to insure that he is properly and skillfully examined; to protect him against the known hazards entailed in topical or general anesthesia; to prevent injudicious instrumentation. And, as a result of such a diagnostic or therapeutic procedure, we must be certain that he will be definitely benefited.

Secondly, we wish to be loyal to both the science and the art of medicine. We are pledged not only to handle his problem in the light

of the most recent proven methods and techniques available, but to avoid delays in performing indicated procedures. We are further pledged to be certain that our armamentarium is in proper and efficient working order and, also, to explain sufficiently to the patient and his family the reasons for what we propose to do. Only in this way can they both understand us and trust us. To be ethical we ask for consultation whenever we feel the patient or his family desires another opinion; or when the problem is such that we wish the added support of a colleague's opinion; or when our own ability to handle a particularly difficult problem is not yet developed to the point where we would willingly assume the entire responsibility. Our loyalty here also extends to the hospital and the hospital staff with whom we work. Our liaison with the thoracic surgeon can be a highly cooperative endeavor for high quality patient care—or it can be a frequent source of friction if we allow it.

Our third loyalty is to the younger physicians in training. We want to teach them actively by precept and to instruct them carefully in the endoscopic techniques in which we are skilled. Only by such effort can we insure a continued high quality of patient care in the years to come.

Fourthly, our loyalty to our specialty often is misconstrued by us due to frequent and sudden needs for policy decisions. I am unaware of any limitation of the practice of broncho-esophagology to any particular specialty group or to otolaryngologists only in our Association's constitution. Let me read you the succinct paragraph from our constitution which describes the object of our Association. "The object of this Association shall be: the promotion of the knowledge of diseases and injuries in the respiratory and upper digestive tracts, and of borderline conditions; their diagnosis and treatment by means of direct or indirect inspection; cooperative effort with the allied specialties; the fostering of friendly assembly and of scientific stimulation among its members; the advancement of the art of broncho-esophagology."

Domestic policy is best reflected in the local city and hospital interdependence.

With these broad principles in mind, consider what has happened historically in a single city since the first endoscopic procedure was performed there by Dr. Thomas Halstead, one of the pioneer men in this field in the country. Hoople[1] has recounted the difficulties encountered by individual otolaryngologists in Syracuse, New York, in obtaining equipment and operating room facilities. This led them to combine the few instruments they each had available and to set up

an endoscopic clinic in the Syracuse Memorial Hospital. At that time, in 1935, it had the largest operating suite in the city. Foreign body work comprised the majority of the procedures at first, since none of the general surgeons or internists were then greatly interested in this facet of medical diagnosis and treatment. As the clinic grew, the treatment of asthmatics opened broader diagnostic possibilities and, after remaining stable for four years with about 190 patients per year, in the fifth year clinic attendance nearly doubled.

Since this report, Syracuse has weathered the sudden dearth of physicians occasioned by World War II; has seen the clinic carried on most effectively by one of our former members, Dr. Irl H. Blaisdell, whose enormous capabilities were lost to the profession and his community by his tragic death; has benefited by the advances in new techniques developed during this wartime period of urgent and heroic medicine. Further, it has become the third most rapidly growing city in the country.

It is now evident that co-operation among otolaryngologists alone is not enough. All whose interests or efforts touch the field of endoscopy must co-operate, or else the patient does not fully benefit.

The addition of a thoracic surgeon to a hospital staff, intermittently co-operative hospital administration, frequent lack of well trained nursing personnel, inadequate follow-up of patients due to pressure of otolaryngological practice, and the entrance of the federal government into quasisocialized medicine through its Veterans' Administration Hospital policies—all of these may be problems of yours, too.

Our first thoracic surgeon came to Syracuse in 1945 and was invited to participate in the endoscopic clinic. He willingly agreed to meet weekly in conference with the bronchoscopic clinic staff and radiologists for the purpose of evaluating patients for possible thoracic surgery. In addition, he is a well trained endoscopist. In 1953, his practice required the addition of a younger associate. In 1954, the total number of endoscopic procedures using the clinic facilities was only 1/6 larger than in 1940. Yet, more than 1/3 of the procedures were done by the thoracic service. The Veterans' Hospital and one other large hospital were not included.

With these factors still in mind, take off your headmirror for a moment and think of yourself as a general practitioner. Mrs. Jones, age 42 with many family responsibilities, especially five children, has had two episodes of pneumonia in the last year and a half and chest findings are suspicious of a pulmonary lesion underlying the infectious process. You are unfamiliar with the most recent thoracic surgical

tenets for determining operability of such a lesion if found. Radiological consultation reveals the presence of atelectasis of the right middle lobe enhancing the possibility of an underlying lesion. The left lung field is not entirely clear and the radiologist raises the question of bronchiectasis because of the increased markings. There are ten otolaryngologists in your community and one thoracic surgeon. He does his own endoscopies. Should you request bronchoscopy by the otolaryngologist or the total opinion of the thoracic surgeon? The endoscopist who gives you a "normal findings in the tracheobronchial tree" brings you little nearer to a concrete decision. Your own knowledge of chest operability is meager and leaves you little alternative as to seeking a thoracic surgical opinion regarding this. You are acutely aware of the patient's heavy financial load with five children in the family, and you are no nearer a definitive decision as to how best to advise your patient after a normal findings examination. I certainly could not take strong issue with you for by-passing the otolaryngologist and immediately asking for a thoracic opinion.

On the other hand, a child who has inhaled a foreign body, a head injury case in respiratory difficulty, an older patient with pneumonia and collection of secretions in the trachea, a polio patient with progressing bulbar signs, a child with acute laryngotracheobronchitis, all who need special tracheal care and who may require tracheotomy and the attendant close supervision of one skilled in this procedure—these you refer at once and without hesitation to the trained otolaryngologist.

Frequently, desired changes in hospital policy which would produce more efficient bronchoscopic clinic handling of patients, has met with delay. At other times, hospital administration has been very cooperative. The status quo, more pay, shorter hours, and an increasing difficulty in budget balancing has complicated administrative attempts to consider the patient first.

When the clinic started, it was necessary to transfer to the Memorial Hospital all patients for this examination. They were then returned to the original hospital. Ambulatory cases were handled on an out-patient basis. Patient inconvenience and the desires of other hospital staffs led four additional hospitals to procure specialized equipment to do some or all of this work.

How recently have you encountered the same shortage of nurses and rapid turn-over of specially trained nursing personnel that we have noted? This has, unfortunately, interrupted our program of sending carefully selected individuals to one of the large centers for a week or two of postgraduate nursing training in bronchoscopic

operating room techniques. Our instrumentarium has suffered drastically because of this and even frequent large scale inventories and repairs have failed to allow the endoscopist the proper instrument in good working order when he needs it in an emergency.

While providing strictly a consultation type of service, our lack of follow-up on patients puts us at a disadvantage. The pressures of busy ear, nose, and throat practice, teaching programs, and curricular interests draw us away from the follow-up telephone calls to the referring physician or hospital service.

In 1953, the Veterans' Administration built and equipped a 500 bed Dean's Committee Hospital on a site adjacent to the Medical College. Teaching facilities are available and, at present, more endoscopies are encountered here in the resident training program by far than in all the other hospitals affiliated with the center in our work.

Unwittingly, Congress passed legislation which later allowed interpretation to condone, without any practical recourse for investigation, care of any veteran for a nonservice connected disability. This not only appears to over-extend veterans' benefits, but firmly sets the Government into unfair competition rather than co-operation with private hospitals, and initiates socialized medicine for an ever enlarging number of veterans.

In conclusion: As mature practitioners of medicine we have, this afternoon, related the open door policy and the field of endoscopy. We have observed that cooperation must be the keynote of both our foreign and our domestic policy if we are to fulfill our loyalties to our patient, our profession, our students and our American Broncho-Esophagological Association.

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XLVI

SURGICAL REPAIR OF THE CERVICAL TRACHEA FOLLOWING TRAUMA

A CASE REPORT

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Many investigators[1-14] have tried to determine the best method for surgical repair of partial or total surgical defects in the tracheas of dogs and humans. These workers have shown that partial defects in the cervical or thoracic trachea can be repaired by the use of fascia lata, fibrin gel, dermografts, soft tissue grafts, and tantalum gauze. It was found that respiratory epithelium will line the tracheal lumen surface of the defect. Stenoses are rare in these instances. When there is a sleeve-like or total loss of the trachea, the best method of repair has been found to be end-to-end anastomosis, provided there is not undue tension on the cut tracheal ends and the blood supply is adequate. A total loss of a large segment of the trachea in which an end-to-end anastomosis is impossible has been repaired experimentally by many different methods. Various prostheses used in the repair of these defects have been Vitallium tubes, stainless steel tubes, polyethylene tubes, Nobilium tubes, glass tubes, preserved tracheal cartilage, decalcified bone or partially decalcified bone, split thickness grafts, and full thickness rib and muscle grafts. From these experiments it can be stated that there is no one satisfactory method for replacing large sections of the trachea either in dogs or humans.

It is interesting to point out the various methods that have been employed in humans for repair of the cervical trachea. As early as 1927 Fairchild[15] reported the case of a 20 year old male with a neck injury in an automobile accident whose cervical trachea was successfully repaired by the use of full thickness pedicle and sliding grafts from the neck and chest. In 1928 Arbuckle[16] reported the successful use of skin grafting within the larynx for stricture. Figi[17] also reported the use of split thickness grafts for stenoses of the larynx. In 1945 Erich[18] also used skin grafting for strictures of

From the Otorhinolaryngology Department, Fort Miley Veterans Hospital.

the larynx and upper trachea. These authors noted that split thickness skin grafts would live in the denuded stricture areas and that the new lumen would remain patent and functional provided there was rigid support. Longmire[19] reported the case of a ten year old boy who had a loss of a portion of the cervical trachea following trauma. Even after repair and the use of an acrylic dilator for months, the newly formed airway collapsed because of lack of rigid support. Paulson[20] reported plastic reconstruction of part of the upper cervical trachea for an inflammatory stricture following tuberculosis. He repaired the defect by a dermal graft reinforced by stainless steel wire. Harkins[21] reported the use of a Nobilium cylinder which he inserted into the trachea of a 14 year old white female who had a stenosis following diphtheria at the age of three years. Rob and Bateman[22] reported an interesting case where the cervical portion of the trachea was almost totally removed for neoplasm and that closure was done by using tantalum gauze which was covered on both sides by fascia lata. The tantalum gauze with its fascial coverings was fashioned as a hollow cylinder. This patient was seen a year later and was noted to have a successful reconstruction of the upper trachea. Edgerton and Zovickian[23] reported the successful use of skin grafting of the upper trachea and larynx in cases of stricture. They further reported the successful repair of a loss of a part of the cervical trachea by sliding full thickness grafts from the chest. Support in the newly created tracheal wall was fashioned by the use of a metal stent. Kay[24] reported that he removed a leiomyoma of the upper trachea of a female patient and repaired the defect by end-to-end anastomosis.

In this series of patients noted above, surgical repair of the cervical trachea was done in three types of cases; namely, in patients with traumatic disruption of the cervical trachea and loss of tracheal substance, in patients with resectable neoplasms of the cervical trachea, and finally in patients with inflammatory strictures after the inflammatory process was quiescent.

In order for the surgical repair of the cervical trachea to be successful, the larynx and distal tracheobronchial pulmonary systems must function adequately.

If one is faced with the problem of a patient with injury to the cervical trachea, the most immediate problem is to establish an adequate airway by tracheotomy. The tracheostomy should be placed distal to the lower tracheal segment if possible. Once tracheotomy is done and the patient's respirations are assured, an end-to-end anastomosis is a treatment of choice, provided there is no contraindication to definitive surgery, and provided that the anastomosis can be done without undue tension and without jeopardizing the blood supply of

the cut ends of the trachea. The distally placed tracheostomy should be maintained postoperatively. If end-to-end anastomosis is impossible, then the methods of tracheal repair vary and one cannot definitely state which method of repair is most satisfactory for the individual case.

The objectives to strive for in creating a functional cervical trachea may be listed as follows: adequate airway, tracheal support, epithelial lined airway, and the prevention of stricture and collapse. These cannot be attained in all cases.

It is the purpose of this paper to report the case of a male who suffered a traumatic injury to the cervical trachea.

REPORT OF A CASE

E.T.H., aged 27 years, was injured in an airplane accident on July 4, 1949. He sustained a crushing injury to the anterior portion of the neck. The airplane accident occurred in Idaho and he was taken to a local hospital where a tracheotomy was performed immediately. Ten days later the first three crushed tracheal rings were removed surgically and an attempt was made to do an end-to-end anastomosis of cricoid cartilage to the lower tracheal stump. The tracheotomy tube was removed. The patient had difficulty in breathing and ten days later bronchoscopy was done because of a developing stricture in the repaired area. Tracheotomy was done again. The tracheotomy tube was left in place for two and one-half months and during this period of time a fibrotic stricture developed in the area of the trachea where the first three tracheal rings had been removed. Still in Idaho in October 1949, the patient had a Vitallium tube placed in the upper trachea after excision of the scar. The tube was three-fourths inch long and nine-sixteenths inch in diameter and was anchored to the surrounding tissues by wire sutures. The tracheotomy tube was again removed. Since granulation tissue obstructed the lumen of the Vitallium tube, the patient had to be bronschoscoped at two week intervals to have it removed. The patient was then sent to the Veterans' Hospital in Boise, Idaho, in February 11, 1950, eight months after the original injury. Two days after admission to the Veterans' Hospital in Boise, a tracheotomy was done again. On March 31, 1950, still at the Veterans' Hospital in Boise, the Vitallium tube was removed and was replaced by a stainless steel tube measuring 1⅛ inches long. This tube had a longitudinal ridge on its side for anchoring wire sutures (Fig. 1). During the course of the next few weeks, the patient was again without the use of a tracheostomy and was breathing through the lumen of the stainless steel tubing and the larynx. Six bronchoscopies were done during this

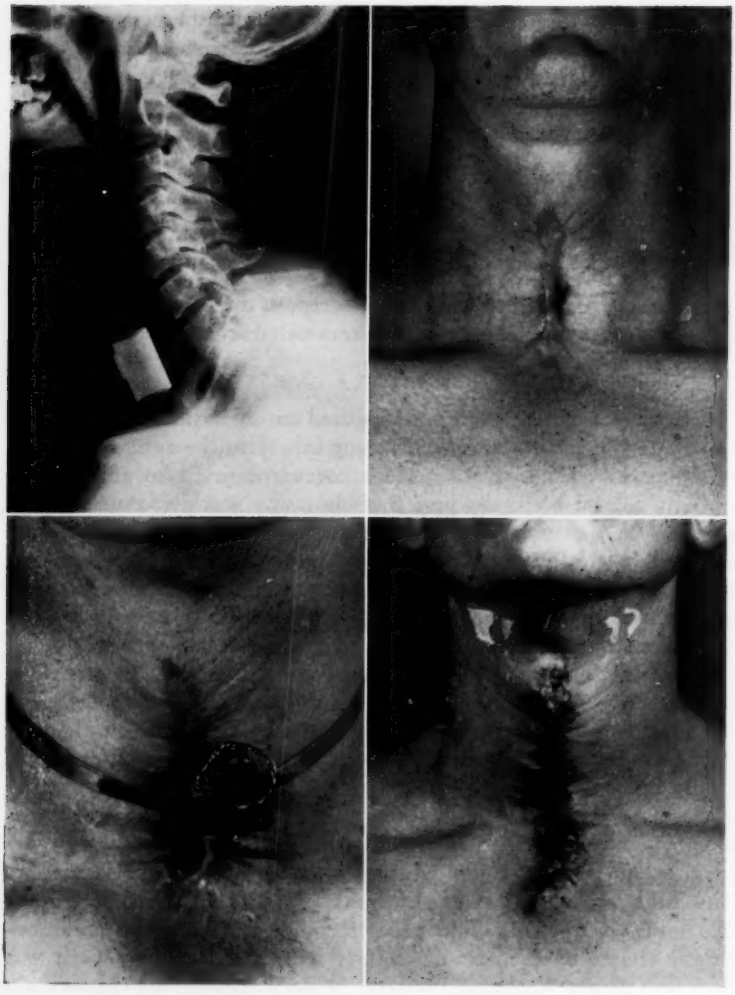

Fig. 1.—This lateral roentgenogram shows the stainless steel tubing in place. Note the ridge and eyelets for wire sutures. Further note the absence of a tracheotomy tube.

Fig. 2.—Appearance of the patient's neck August 20, 1950, thirteen months after original injury. Three attempts had been made elsewhere during this period of time to repair the patient's cervical trachea.

Fig. 3.—This photograph shows the patient's neck and the steel wires which were used to anchor the acrylic dilator. Note that the neck wound has healed even though the trachea, graft, and dilator were "exteriorized."

Fig. 4.—This photograph shows the patient's neck a few days after secondary closure of the whole wound including the tracheostomy site. The patient's neck healed per primam.

period of time to remove granulation tissue from the lumen of the stainless steel tube. His condition was only partially satisfactory because he was losing weight and was unable to breathe properly.

The patient was transferred to Fort Miley Veterans' Hospital on August 18, 1950, and this was the first contact that the undersigned had with the patient (Fig. 2). The day after admission, bronchoscopy was done and granulation tissue was removed from the lumen and ends of the stainless steel tubing. At this time the larynx itself was found to be perfectly normal, the vocal cords moved and there was an adequate glottic chink. Just below the cricoid cartilage, the stainless steel tubing could be identified easily (Fig. 5). Two subsequent bronchoscopies were done and granulation tissue was removed. On September 19, 1950, the stainless steel tubing was removed by opening the neck vertically. A low tracheostomy was done through the fifth tracheal ring. Since the patient had had three previous attempts at tracheal repair, it was decided to put a rubber tube through the strictured area to see if the granulation tissue would cover with epithelium. The rubber tube extended just below the true vocal cords. A tracheotomy tube was left in place. When the stainless steel tubing was removed and the rubber tubing inserted, it was noted that there was an absence of the first three tracheal rings and that there was dense scar and granulation tissue at this site. On November 27, 1950, the patient coughed the rubber tube out in spite of its being anchored to the tracheotomy tube. Bronchoscopy was done three days later and it showed that there was no improvement in the strictured area of the trachea and that granulation tissue was still present. The patient was allowed a rest period and on January 31, 1951, the neck was again re-opened and a dense stricture was found where the upper three tracheal rings were absent. Scar and granulation tissue was excised in this area. It was noted further that the remaining scar had a dense character and might act as a support for a tracheal wall. A split thickness skin graft was then inserted into the strictured area and held in place by a sterile sea sponge and stainless steel wires (Fig. 6). At this time an impression of the strictured area was made with red dental compound so that an acrylic dilator could be fashioned (Fig. 9). Ten days after the sea sponge and graft were inserted in the upper trachea, the sea sponge was removed by opening the neck wound and the acrylic dilator was inserted into the area that had been previously grafted. The skin graft appeared healthy. By using large stainless steel wires, the acrylic dilator was anchored and the found was left wide open and in a sense the trachea was exteriorized (Fig. 3). The acrylic dilator and tracheotomy tube were worn constantly by the patient for a period of six months (Fig. 7). On July 24, 1951, the wound was reopened and the acrylic

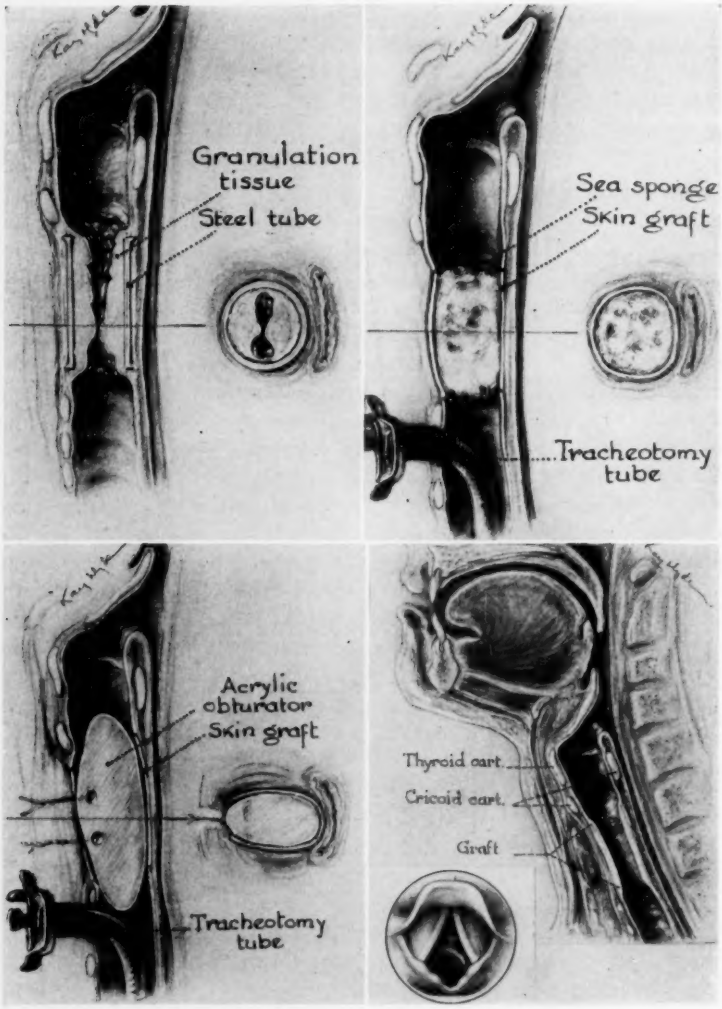

Fig. 5.—This drawing shows the stainless steel tube in place. Note that granulation tissue has grown in from both ends of the tube. Since this is an artist's conception, no areas of bare tubing are depicted. However, at bronchoscopy it was noted that the inside of the tubing was not completely covered with granulation tissue. It was found growing at each end of the tube and was encroaching into the lumen thus reducing the patient's airway.

Fig. 6.—Artist's conception of grafter area of upper cervical trachea with sea sponge holding graft. Note tracheostomy in fifth tracheal ring.

Fig. 7.—This drawing shows the skin graft, acrylic dilator, and tracheotomy tube in place. The patient wore the dilator comfortablye for six months.

Fig. 8.—These drawings depict the patient's postoperative airway.

dilator was removed. The only granulation tissue noted was anteriorly where the trachea had been exteriorized. At this time the skin edges and subcutaneous tissues were freshened and sutured. The tracheotomy tube remained in situ. Approximately six weeks later and again in twelve weeks a 7 mm bronchoscope passed the strictured area with ease. On November 1, 1951, approximately three and one-half months after the acrylic dilator had been removed, a secondary closure of the tracheotomy was done. The secondary closure also included the removal of scar tissue from the whole anterior portion of the neck (Fig. 4). The neck wound healed per primam and the patient's airway remained adequate. On February 27, 1952, the patient was readmitted to the hospital and a 7 and 8 mm bronchoscope passed the strictured area with ease. There was no evidence of granulation tissue and the lumen of the trachea appeared perfectly adequate. The area of tracheal repair was somewhat smaller than a normal trachea; however, there was no evidence of redundancy or collapse (Fig. 8). The patient was again seen on March 11, 1953, 26 months after the last repair of the trachea. At that time he stated he had no problems of breathing, was working, and had gained weight. Clinical examination confirmed that he was progressing as stated. Bronchoscopy was not done at that time.

On March 25, 1956, the patient was readmitted to Fort Miley Veterans' Hospital. Interval history showed that the patient has been healthy and working as a truck driver. He stated that his breathing was normal. On rare occasions he coughs up a small mucus crust. Physical examination showed the chest to be clear and the neck scar well healed. Indirect mirror examination of the larynx showed a normal glottis and normal movements of the vocal cords. The area of repair of the trachea could be only partially visualized by this method. A roentgenogram of the chest was normal. On March 28, 1956, bronchoscopic examination was done using local anesthesia. Upon introducing a 7 mm standard Jackson bronchoscope through the glottis, the area of repair of the trachea was visualized. The skin graft appeared healthy and was without crusts. The lumen through this area was slightly ovoid in the anterior-posterior diameter but entirely adequate. The bronchoscope passed the repair area without gripping. The remaining examination of the tracheobronchial tree was entirely normal. The 7 mm bronschoscope was withdrawn and a 9 mm standard Jackson bronschope was introduced through the glottis. This bronchoscope also passed the repaired area of the upper trachea, only there was a slight gripping sensation at the end of the bronchoscope but not gripping was noted along the shaft of the instrument. There was no gripping of the bronchoscope upon withdrawal. From these follow-up examinations it is evident

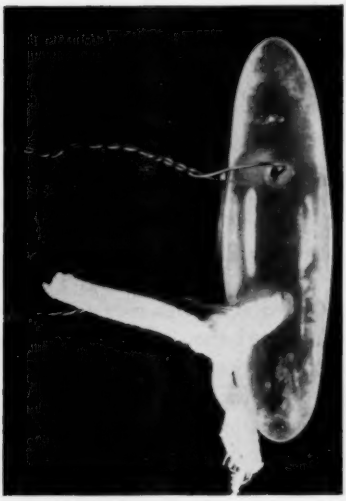

Fig. 9.—The acrylic dilator was fashioned after the impression was made from red dental compound. Note the heavy caliber of the stainless steel wires in the dilators' eyelets. The gauze tape was removed before insertion of the dilator.

that surgical repair of the cervical trachea in this case has been satisfactory and that the patient has been leading a normal life during the past five years.

COMMENT

This case represents some interesting phases of treatment before a successful surgical repair of the trachea was finally accomplished. First and foremost the patient's life was saved immediately following the injury by doing an emergency tracheotomy. Ten days after injury, three crushed tracheal rings were removed surgically and an end-to-end anastomosis was done which subsequently proved unsuccessful. Following this two attempts were made to repair the tracheal defect by the use of Vitallium and stainless steel tubes and both failed because of the formation of scar and granulation tissue at the ends of the tubes. It is pointed out that the patient did not have a tracheotomy tube in place during these three attempts at surgical repair of the strictured area. From examination of the patient's record and noting the treatment that the patient had elsewhere, it was evident that the patient had worn either the Vitallium tube or the stainless

steel tubing during a period of approximately one year. It is surmised that during this period of time the patient developed a certain amount of rigidity of the tracheal wall. One can only speculate whether this rigidity resulted from the formation of dense scar tissue or new cartilage.

SUMMARY

Surgical repair of the trachea is reported in a patient who received a crushing injury and loss of substance of the upper cervical trachea. Late repair of the trachea was successful after the use of split thickness skin grafts probably because the missing tracheal wall had developed sufficient support during the course of treatment elsewhere.

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SIXTH INTERNATIONAL CONGRESS OF OTOLARYNGOLOGY

PRELIMINARY PROGRAM

SUNDAY, MAY 5, 1957

8:30 a.m.-4:00 p.m.

Registration, Presidential Ballroom, Hotel Statler
Scientific and Technical Exhibits open
Hospitality Lounge for Foreign Members open
Ladies' Committee Hospitality Lounge open

5:00 p.m.

Convocation, Constitution Hall

6:00 p.m.

President's Reception and Buffet Supper, Pan American Union (Informal)

MONDAY, MAY 6

8:30 a.m.-5:00 p.m.

Registration, West Checkroom, Hotel Statler
Exhibits open
Hospitality Lounges open

Open each day during these hours

9:00 a.m.-12:00 noon

Plenary Session, Presidential Ballroom, Hotel Statler

CHRONIC SUPPURATION OF THE TEMPORAL BONE

Openers: PROF. MARCUS DIAMANT, Halmstad, Sweden
Anatomical and Etiological Factors in Chronic Middle Ear Disease

PROF. LUZIUS RÜEDI, Zürich, Switzerland
Pathogenesis and Treatment of Cholesteatoma in Chronic Suppuration of the Temporal Bone

PROF. HORST WULLSTEIN, Würzburg, Germany
Surgical Repair for Improvement of Hearing in Chronic Otitis Media

Discussers: Mr. A. Tumarkin, F.R.C.S., Liverpool, England
Prof. Juan Manuel Tato, Buenos Aires, Argentina
Mr. T. E. Cawthorne, F.R.C.S., London, Eng.
Prof. Fritz Zöllner, Freiburg, Germany

Sightseeing tours in and about Washington (available daily)

MONDAY, MAY 6 (continued)

2:00-5:00 p.m.

General Sessions, 5 simultaneous sections (rooms to be designated)
Film Session, Presidential Ballroom
Sightseeing tours (available daily)
Medical tours to Walter Reed Army Medical Center
Armed Forces Institute of Pathology
Navy Medical Center, Bethesda, Maryland
National Institutes of Health, Bethesda
Forest Glen Speech and Hearing Center
(These tours available each afternoon)

8:00 p.m.

Reception and tour, National Gallery of Art

TUESDAY, MAY 7

9:00 a.m.-12:00 noon

General Sessions, 5 simultaneous sections
Film Session, Presidential Ballroom
Special all-day program for ladies including tour and luncheon

2:00-5:00 p.m.

General Sessions, 5 simultaneous sections
Film Session, Presidential Ballroom
Special ladies' program continued during afternoon

8:30 p.m.

Concert, Constitution Hall
Program of musical Americana

WEDNESDAY, MAY 8

9:00-9:30 a.m.

Special address, Presidential Ballroom

DOCTORS AS DIPLOMATS

Howard Rusk, M.D., Director, Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, New York

9:30 a.m.-12:30 p.m.

Plenary Session, Presidential Ballroom

COLLAGEN DISORDERS OF THE RESPIRATORY TRACT

Openers: PROF. HANS SELYE, Montreal, Canada
Introduction

PROF. MICHELE ARSLAN, Padua, Italy
The Upper Respiratory Tract

DR. LESLIE GAY, Baltimore, Maryland
The Lower Respiratory Tract

Discussers: Sir Victor Negus, London, England
Prof. Branimir Gusic, Zagreb, Yugoslavia
Dr. Aubrey G. Rawlins, San Francisco, California, U.S.A.
Dr. Henry L. Williams, Rochester, Minnesota, U.S.A.

2:00-5:00 p.m.

General Sessions, 5 simultaneous sections
Film Session, Presidential Ballroom

5:00-6:00 p.m.

Business meeting, International Committee (Official Delegates)

6:00-7:00 p.m.

Dinner for Official Delegates and wives, South American Room (formal)

THURSDAY, MAY 9

9:00 a.m.-12:00 noon

General Sessions, 5 simultaneous sections
Film Session, Presidential Ballroom

2:00-5:00 p.m.

General Sessions, 5 simultaneous sections
Film Session, Presidential Ballroom

7:00-8:00 p.m.

Congress cocktail party, Sheraton-Carlton Hotel

8:15 p.m.

Grand Banquet, Presidential Ballroom and Congressional Room, Statler Hotel (formal)

FRIDAY, MAY 10

9:00 a.m.-12:00 noon

Plenary Session, Presidential Ballroom

PAPILLOMA OF THE LARYNX

Openers: Prof. Jo Ono, Tokyo, Japan
Etiology

Prof. Plinio de Mattos Barretto, Sao Paulo, Brazil
Diagnosis

Mr. F.C.W. Capps, London, England
Therapy

Discussers: Prof. C. A. Hamberger, Göteborg, Sweden
Dr. Pedro Hernandez Gonzalo, Havana, Cuba
Prof. Eelco Huizinga, Groningen, Netherlands
Prof. Albert von Riccabona, Vienna, Austria

2:00-5:00 p.m.

General Sessions, 5 simultaneous sections
Film Session, Presidential Ballroom

The following activities will be scheduled every day:

8:30-5:00

Registration
Scientific Exhibits
Technical Exhibits
Hospitality Lounge for Foreign Members
Ladies' Committee Hospitality Lounge

Morning and afternoon
Hours to be announced
Sightseeing tours

Each afternoon
Hours to be announced
Medical tours

Notices

ACADEMY HOME STUDY COURSES

The 1956-1957 Home Study Courses in the basic sciences related to ophthalmology and otolaryngology, which are offered as a part of the educational program of the American Academy of Ophthalmology and Otolaryngology, will begin on September 1 and continue for a period of ten months. Detailed information and application forms can be secured from Dr. William L. Benedict, the executive secretary-treasurer of the Academy, 100 First Avenue Building, Rochester, Minnesota. Registrations should be completed before August 15.

AMERICAN LARYNGOLOGICAL ASSOCIATION

Copies of the Transactions of the American Laryngological Association are available for general distribution at $8.00 a copy. Please send request with check to:

Dr. Edwin N. Broyles,
Editor Transactions
1100 North Charles St.
Baltimore 1, Md.

AMERICAN BOARD OF OTOLARYNGOLOGY

The American Board of Otolaryngology will conduct an examination October 8-11, 1956, in Chicago, Illnois, at the Palmer House.

WASHINGTON UNIVERSITY

The Department of Otolaryngology, Washington University, Saint Louis, offers a Basic Science Course in Otolaryngology to start on Monday, September 17, 1956. Complete information about the course may be obtained by writing to the Head of the Department of Otolaryngology, 640 S. Kingshighway, St. Louis 10, Missouri.

TULANE UNIVERSITY OF LOUISIANA
SCHOOL OF MEDICINE

The three year residency in otolaryngology offered at Charity Hospital of Louisiana at New Orleans on the Tulane University of Louisiana School of Medicine service is designed to qualify the holder for the examinations of the American Board of Otolaryngology and the practice of all phases of otolaryngology and endscopy.

Candidates must be graduates of a class A medical school and must have completed a minimum of one year of general internship. An additional year of residency in internal medicine or general surgery is desirable but not essential.

All work is under the direct supervision of members of the Tulane Department of Otolaryngology, who are also members of the Charity Hospital Otolaryngological Staff; they are available at all times for instruction and guidance. Basic sciences are offered throughout each year of the residency during the academic year. The resident also participates in the program of the Speech and Hearing Center at the Tulane University School of Medicine.

The hospital year extends from July 1 of one year to June 30 of the following year.

Applications should be addressed to the Chairman of the Department of Otolaryngology, Tulane University of Louisiana School of Medicine, 1430 Tulane Ave., New Orleans 12, Louisiana.

TEMPLE UNIVERSITY
SCHOOL OF MEDICINE AND HOSPITAL

The following courses are all to be given in the Department of Laryngology and Broncho-Esophagology, Temple University Hospital and School of Medicine, under the direction of Drs. Chevalier L. Jackson and Charles M. Norris:

Postgraduate Course in Broncho-Esophagology, February 6-17, 1956; May 28-June 8, 1956; September 17-28, 1956.

Postgraduate Course in Laryngology and Laryngeal Surgery, April 23-May 4, 1956; November 5-16, 1956.

The tuition fee for each course is $250.00.

Further information and application blanks can be obtained from Dr. Chevalier L. Jackson, 3401 N. Broad St., Philadelphia 40, Pa.

COLLEGIUM OTO-RHINO-LARYNGOLOGICUM AMICITIAE SACRUM

The Shambaugh Prize of the Collegium Oto-rhino-laryngologicum for 1955 has been awarded to Charles Skinner Hallpike of London in recognition of his outstanding research on the vestibular and acoustic labyrinth.

The Shambaugh Prize was founded in memory of the late Dr. George E. Shambaugh, Sr. by his family and is awarded every second year. Previous recipients of the prize are Dr. G. von Békésy, Dr. Raoul Caussé and Dr. Hallowell Davis.

UNIVERSITY OF ILLINOIS

The next course in Laryngology and Bronchoesophagology to be given by the University of Illinois, College of Medicine, is scheduled for the period November 5 through November 17, 1956. The course is under the direction of Dr. Paul H. Holinger.

Interested registrants will please write directly to the Department of Otolaryngology, University of Illinois, College of Medicine, 1853 W. Polk Street, Chicago 12, Ill.

The Department of Otolaryngology, University of Illinois College of Medicine, announces its Annual Assembly in Otolaryngology from October 1 through 7, 1956. The Assembly will consist of an intensive series of lectures and panels concerning advancements in otolaryngology, and evening sessions devoted to surgical anatomy of the head and neck and histopathology of the ear, nose and throat.

Interested physicians should write direct to the Department of Otolaryngology, 1853 West Polk Street, Chicago 12, Illinois.

THE NINTH ANNUAL CONFERENCE ON ELECTRICAL TECHNIQUES IN MEDICINE AND BIOLOGY

The Ninth Annual Conference on Electrical Techniques in Medicine and Biology will be held at the Governor Clinton Hotel in New York City on November 7, 8, and 9, 1956.

The Conference is sponsored by the American Institute of Electrical Engineers, the Institute of Radio Engineers, and the Instrument Society of America. In addition to the technical sessions, there will be field trips to installations of interest to those attending.

Titles and brief abstracts for proffered papers may be submitted to the Conference Chairman, E. Dale Trout, General Electric Company, X-Ray Department, Milwaukee 1, Wisconsin.

YALE UNIVERSITY ONE-DAY CONFERENCE

A special one-day Symposium on Occupational Noise will be held at Yale University - New Haven Medical Center on September 17, 1956. Information concerning this program may be obtained by writing to the Assistant Dean of Postgraduate Medical Education, Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn.

ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY

In order to complete the interrupted files of some foreign libraries, the ANNALS will buy from subscribers a certain number of the following issues now out of print. Please communicate with the Business Manager, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY, P. O. Box 1345, Central Station, St. Louis 1, Mo., U.S.A.

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June 1955
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OFFICERS

OF THE

NATIONAL AND INTERNATIONAL OTOLARYNGOLOGICAL SOCIETIES

VI International Congress of Otolaryngology

President: Arthur W. Proetz, M.D., St. Louis, U. S. A.
Secretary-General: Paul H. Holinger, M.D., 700 North Michigan Ave., Chicago 11, Ill., U. S. A.
Meeting: Washington, D. C., May 5-10, 1957.

International Bronchoesophagological Society

President: Dr. Julio Cesar Barani, Montevideo
Secretary: Dr. Chevalier L. Jackson, 3401 N. Broad St., Philadelphia 40, Pa.
Meetings: Vienna, August 31-September, 1956; Philadelphia, May 12 and 13, 1957.

Pan-American Association of Oto-Rhino-Laryngology and Broncho-Esophagology

President: Dr. Jose Gros, Havana
Secretary: Dr. Chevalier L. Jackson, 3401 N. Broad St., Philadelphia 40, Pa.
Meeting: Brazil, 1958.

American Academy of Ophthalmology and Otolaryngology

President: Dr. Algernon B. Reese, New York.
Executive Secretary: Dr. William L. Benedict, Mayo Clinic, Rochester, Minn.

American Board of Otolaryngology

President: Dr. Gordon D. Hoople, Syracuse, N.Y.
Secretary: Dr. Dean M. Lierle, University Hospital, Iowa City, Iowa.
Next examination: Chicago, October 8-11, 1956.

American Broncho-Esophagological Association

President: Dr. Clarence W. Engler, Cleveland, O.
Secretary: Dr. F. Johnson Putney, 1719 Rittenhouse Sq., Philadelphia 3, Pa.
Meeting: None, in 1957.

American Laryngological Association

President: Dr. LeRoy A. Schall, Boston.
Secretary: Dr. Harry P. Schenck, 326 South 19th St., Philadelphia, Pa.
Meeting: Hotel Statler, Washington, D.C., May 3, 1957.

American Laryngological, Rhinological and Otological Society, Inc.

President: Dr. Dean M. Lierle, Iowa City.
Secretary: Dr. C. Stewart Nash, 708 Medical Arts Bldg., Rochester, N. Y.
Meeting: None, in 1957.

American Medical Association, Section on Laryngology, Otology and Rhinology

Chairman: Dr. John R. Lindsay, Chicago, Ill.
Secretary: Dr. Hugh A. Kuhn, Hammond, Ind.

American Otological Society

President: John R. Lindsay, M.D., Chicago.
Secretary-Treasurer: Lawrence R. Boies, M.D., University of Minnesota Hospitals, Minneapolis 14, Minnesota.
Meeting: Hotel Statler, Washington, D.C., May 4, 1957.

The American Society of Ophthalmologic and Otolaryngologic Allergy

President: Dean McAllister Lierle, M.D., University Hospital, Iowa City, Iowa.
Secretary: Michael H. Barone, M.D., 468 Delaware Avenue, Buffalo 2, New York.

Pacific Coast Oto-Ophthalmological Society

President: H. Leroy Goss, M.D., 620 Cobb Building, Seattle 1, Wash.
Secretary-Treasurer: Homer E. Smith, M.D., 508 East South Temple, Salt Lake City, Utah.
Meeting: Coronado, California, April 7-11, 1957.